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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 5

DATE: MAR 17 2003

SUBJECT: Approval for Public Release of the Peer-reviewed Work Product Toxicity Reference Values (TRVs) for Mammals and Birds Based on Selected Aroclors

FROM: William E. Muno, Director, SFD

TO: James Chapman, Ecologist, Peer Review Leader

Following internal U.S. EPA peer review in accordance with the 1998 Peer Review Handbook (EPA 100-B-98-001) and the October 2000 Region 5 Order "Improved Policies and Procedures: Peer Review, Records Management, and Work Product Authorization of Scientific and Technical Work Products", and satisfactory revision in response to the peer review comments, the memorandum Toxicity Reference Values (TRVs) for Mammals and Birds Based on Selected Aroclors, dated March 6, 2003, is approved for public release.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 5

DATE: March 12, 2003

SUBJECT: Peer Review Record for Toxicity Reference Values (TRVs) for Mammals and Birds Based on Selected Aroclors

FROM: James Chapman, Ph.D., Ecologist

TO: William Muno, Director, Superfund Division

The peer review record for the development of PCB TRVs for wildlife is attached for your approval.

The following documents are enclosed:

Peer Review Checklists #1 and 2.

The Peer Review Charge for Mink and Chicken PCB Toxicity Reference Values Derived Through an EDx (effective dose) Procedure. The peer review charge conforms with the scope as you directed on 8/22/02, and was sent to the peer reviewers on 10/02/02. The draft work products: Draft Mink PCB Toxicity Reference Value (TRV), 9/24/02, and Revised Avian PCB Toxicity Reference Value (TRV), 9/23/02, the cover email messages (10/02/02), and the supporting documentation sent to the peer reviewers including the linear interpolation tables, PCB toxicity studies tables, relative response tables, and graph data files.

The Responses to Peer Review Comments, Wildlife PCB Toxicity Reference Values, 3/6/03, which presents the consolidated review comments and the responses to the charge questions in accordance with your recommendations of 1/8/03.

The Original Peer Review Comments are attached in alphabetical order of the reviewers: Dr. Chris Cubbison (NCEA), Dr. Tala Henry (ORD), Dr. Dale Hoff (Region 8), Dr. Mark Sprenger (OERR), and Dr. Glenn Suter (NCEA), as received between 10/17/02 and 11/14/02. Two reviewers, Drs. Henry and Suter, submitted additional questions and comments outside of the scope of the peer review charge. The responses to these non-charge comments are also appended in memos dated 10/18/02 and 11/1/02.

The revised work product Toxicity Reference Values (TRVs) for Mammals and Birds Based on Selected Aroclors, 3/6/03, which is revised in accordance with the Responses to Peer Review Comments.

cc: Wendy Carney, Branch Chief
Shari Kolak, Tom Alcamo, RPMs
Tom Short, Section Chief

PR file memo.wpd

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 5

DATE: March 12, 2003

SUBJECT: Transmittal of Peer Review Checklist #2 for Toxicity Reference Values (TRVs) for Mammals and Birds Based on Selected Aroclors prepared for the Allied Paper/Portage Creek/Kalamazoo River Superfund Site in Michigan

FROM: James Chapman, Ph.D., Ecologist

TO: William E. Muno, Director, SFD

Attached to this memorandum is the Peer Review Checklist #2 for the Avian and Mink PCB TRVs prepared for the Allied Paper/Portage Creek/Kalamazoo River Superfund Site in Michigan. The purpose of this checklist is to document completion of each of the required elements of the peer review process.

The checklist has been prepared in accordance with the U.S. EPA Science Policy Council Peer Review Handbook and the October 2000 Region 5 Order "Improved Policies and Procedures: Peer Review, Records Management, and Work Product Authorization of Scientific and Technical Work Products".

Peer Review Checklist #2 – Conducting a Peer Review

Instructions: This checklist is based on the Agency's January 1998 Peer Review Handbook (EPA 100-B-98-001) and the October 2000 Region 5 Order "U.S. EPA Region 5 Improved Policies and Procedures: Peer Review, Records Management, and Work Product Authorization of Scientific and Technical Work Products" which constitute Region 5's standard operating procedures for peer review. If you have any questions about peer review or need clarification when completing this checklist, please refer to the Handbook, available via the internet at http://www.epa.gov/ord/spc/2peerrev.htm. Pages 2-4 of the Handbook contain useful flowcharts and cross references to specific sections of the Handbook that are applicable to this checklist. You are also encouraged to consult with your Division or Office Peer Review Coordinator. The Division/Office Peer Review Coordinators will periodically request information from this checklist in order to update the National Peer Review Database.

1. **Title of Work Product:** Avian and Mink PCB Toxicity Reference Values (TRV); [Toxicity Reference Values (TRVs) for Mammals and Birds Based on Selected Aroclors]

2. **Product Description:** Derivation of PCB TRVs from exposure- or dose-response plots through an EDx procedure (effective dose, x - effect size of concern)

3. **Project Manager:** Shari Kolak, RPM, SFD, 6-6151; James Chapman, SFD, Ecologist, 6-7195
   Name, Organization and Phone Number

4. **Up-front Considerations for Planning the Peer Review:** *Check the box when item is completed*

   a. The Div/Office Director has chosen a peer review leader for the project. ☑
      (Note: The project manager and peer review leader can be the same person.)
      Name of Peer Review Leader: James Chapman
      Phone Number: 312 886 7195
      Organization: SFD

   b. The peer review leader has obtained appropriate peer review training before conducting the peer review. ☑

   c. Key questions and issues have been identified to include in the charge to the peer reviewers. ☑

   d. The Div/Office Records Coordinator has been consulted to insure that all the files, including electronic records, will be created, maintained, retained, and disposed of appropriately and in accordance with Div/Office and Agency procedures. ☑

   e. A formal peer review record or file has been established, and provisions have been made to store any electronic records associated with the work product and peer review. ☑
      Location of Record/File: Superfund Records Center

      Provisions for Electronic Records: Superfund Records Center and James Chapman

Check the box when item is completed or circle the appropriate answer (NA = not applicable)

f. There is a source of adequate funding to pay for external peer review if external peer review is necessary and funding is needed. *(Note: Contracts can be used for peer review services. However, special management controls are required to ensure proper use of these contracts. See Sections 3.6.1- 3.6.9 of the Handbook for details.)* ☐ (NA)

Source of Funding: _____

g. Resource limitations may restrict the peer review. *(If "yes" was selected, a limited peer review might be considered. However, only in very rare circumstances should resource limitations restrict peer review. Peer review must be planned for as part of a project's budget.)* Yes (No)

h. Amount of time needed for peer review(s) has been allotted given existing constraints of potential peer reviewers, deadline for the final work product, logistics for the peer review, etc. ☒

Length of Time Needed: 10 wk

5. Develop the Charge to the Peer Reviewers:

a. A clear, focused charge has been formulated that identifies recognized issues, asks specific questions, and invites comments or assistance. ☒

b. The charge has been included in the peer review record. ☒

6. Select the Peer Review Mechanism:

a. The work product is novel, complex, controversial, or has great cost implications. *(If the answer is "yes" to any of the above, serious thought should be given to conducting an external peer review. If the answer is "no" to all of the above, internal peer review is probably sufficient.)* (Yes) No

b. A determination has been made regarding which components or stages of the work product will be peer reviewed. *(Note: Generally, peer review is recommended for each stage of a product's development.)* ☒

Components to be peer reviewed: Methodology for combining study results, interpolation, and adjustment for 2-year exposure effects

c. A peer review mechanism (e.g., internal, external or a combination of both) has been chosen for the work product or stages of the work product. ☒

Mechanism: Internal peer review

d. The work product either: 1) has been, or is being, generated as part of administrative or civil enforcement activities by U.S. EPA, or 2) likely will be used in the future to support administrative or civil enforcement activities by U.S. EPA. *(If the answer is "yes" to either item above, then the Office of Regional Council (ORC) must be consulted if the Peer Review Leader believes an external peer review is needed or is* (Yes) No

preferable. ORC concurrence should be obtained.)

Check the box when item is completed, or circle yes or no

e. The work product is going to be peer reviewed via a refereed, scientific journal. *(If the answer is "yes," the work product still should be considered for peer review because journal peer review may not cover issues and concerns that the Agency would want peer reviewed in order to support an Agency action.)* Yes (No)

f. Logistics for conducting the peer review (e.g., written comments will be received by mail, or will be collected at a meeting) have been included in the peer review record. ☑

g. The Div/Off Director has concurred with the recommended method of peer review. ☑
   Date of Div/Off Director Concurrence: 8/23/02

h. The concurrence of the Div/Off Director has been included in the peer review record. ☑

7. Determine the Specific Time Line for the Peer Review:

a. A start date for the peer review has been selected. ☑
   Start Date: 10/2/02

b. The amount of time the peer reviewers will be given to conduct the peer review has been determined. ☑
   Number of Days for Review: 12

c. A due date for comments from the reviewers has been selected. ☑
   Due Date: 10/21/02

d. The amount of time necessary to incorporate comments from the peer reviewers into the work product has been determined. ☑
   Number of Days for Revision: 50

e. A deadline for final completion of the work product has been determined. ☑
   Due Date: 1/2/03

8. Select the Peer Reviewers:

a. Advice was sought in developing a list of potential peer reviewer candidates who are independent of the work product and have appropriate scientific and technical expertise. ☑

b. The expertise required for the peer review has been determined. ☑

c. In reviewing the candidates, a balance and a broad enough spectrum of expertise were considered. ☑

d. In reviewing the candidates, any potential conflicts of interest were considered. ☑

Check the box when item is completed

e. The peer reviewers have been selected and the process for selecting the reviewers, including inquiries and resolution of potential conflicts of interest, has been documented and included in the peer review record/file. *(Note: Conflict of Interest Inquiry Forms are available from the Regional and Div/Off Peer Review Coordinators.)* ☑

9. Obtain and Transmit Materials for Peer Review:

a. Instructions have been given to the peer reviewers which ask for written comments in a specified format by the specified deadline that are responsive to the charge. ☑

b. The peer reviewers have been provided with the essential documents, data, and information to conduct their review. ☑
   Date Peer Reviewers Given Charge/Materials: 10/2/02

c. The peer reviewers have been instructed not to disclose draft work products to the public. ☑

d. The peer review record/file contains all the materials given to the peer reviewers. ☑

10. Conduct the Peer Review:

a. Written comments have been received from all peer reviewers. ☑
   Date all comments were received: 11/14/02

b. All clarification or additional information necessary from the peer reviewers is received. ☑

c. The validity and objectivity of the comments have been evaluated. ☑

d. Appropriate experts/staff/managers have been consulted on the potential impacts of the comments on the final work product, the project schedule, and budget. ☑

e. The peer review comments have been included in the peer review record/file. ☑

11. Consider the Peer Review Comments:

a. Decisions have been made regarding which comments are accepted and will be incorporated into the final work product, and which comments will not be incorporated. ☑

b. A memo or other written record has been prepared which responds to the peer review comments and specifies acceptance or, where thought appropriate, rebuttal and non-acceptance. ☑

c. The Div/Off Director has concurred with the decisions and written record on how to incorporate the peer reviewers comments in the work product and on which comments will not be incorporated. ☑
   Date of Div/Off Director concurrence: 1/8/03

Check the box when item is completed, or circle yes or no

d. The concurrence of the Div/Off Director has been included in the peer review record/file. ☑

e. The memo or written record documenting how comments were handled and how the work product was revised has been included in the peer review record/file. ☑

f. The work product has been revised to incorporate the acceptable comments. ☑

g. The peer review performed during the process of developing the work product has been summarized and included in the work product. ☑

h. It is necessary to send the revised work product back to the peer reviewers. *(If the answer is "yes," proceed to item #11i. If the answer is no, proceed to item #12.)* Yes (No)

i. Additional comments are received, evaluated, and incorporated into the work product, and placed in the peer review record. ☐

12. Consider Other Comments:

a. Prior to finalization, the document needs additional internal and/or external programmatic review. *(If the answer is "yes," go to #12b. If the answer is "no," proceed to #13.)* Yes (No)

b. Written comments by programmatic reviewers have been received. ☐

c. Final decisions have been made regarding which comments are accepted and will be incorporated into the final work product, and which ones will not be incorporated. ☐

d. A memo or other written record has been prepared which responds to the programmatic review comments and specifies acceptance or, where thought appropriate, rebuttal and non-acceptance. ☐

e. Div/Off Director has concurred with the decisions and written record on how to incorporate the programmatic comments. ☐
Date of Div/Off Director concurrence:

f. The memo or written record has been included in the peer review record/file. ☐

g. The work product has been revised to incorporate the acceptable programmatic comments. ☐

13. Finalize Work Product and Close Out Peer Review:

a. The work product has been completed. ☑

b. The Div/Off Director has approved the work product. ☑
Date of Div/Off Director Approval: 3/17/03

c. The Div/Off Director approval has been included in the peer review record/file. ☑

Check the box when item is completed, or circle yes or no

d. The Div/Off Director has judged the work product to be sufficiently controversial, of significant enough interest to outside parties, or of wide enough distribution, such that it should also be authorized by the Regional Administrator (RA), or the Deputy RA (DRA). *(If the answer is "yes," proceed to #13e. If the answer is "no," proceed to #13f.)* Yes (No)

e. The RA or DRA has authorized the work product. ☐
Date of RA or DRA Authorization: N/A

f. The final work product has been included in the peer review record/file. ☐

14. Publication and Release of Reports:

a. The Div/Off Director has approved publication or release of the work product. ☑

b. The written approval by the Div/Off Director has been included in the peer review record/file. ☒

c. The Div/Off Director has judged the work product to be sufficiently controversial, of significant enough interest to outside parties or of wide enough distribution, such that its distribution or release should also be authorized by the RA or DRA. *If the answer is "yes," proceed to #14d. If the answer is "no," proceed to #15. (Note: The Div/Off Director's decision to elevate to the RA or DRA can be made concurrently with item #13d.)* Yes (No)

d. The RA or DRA has authorized distribution or release of the work product. ☐
Date of RA or DRA Authorization: N/A

15. Retention of Peer Review Files and Records:

a. The Div/Off official procedures for administrative records and the Agency's record retention schedules have been examined to determine how long the peer review record/file, including electronic records, should be retained. *(Note: The required time of retention for final reports and supporting data varies depending upon the nature of the report, however, final reports which are mission related or have an EPA number and receive external distribution are generally permanent federal records.)* ☒

b. The Div/Off Records Officer or the Regional Records Officer has been consulted to help determine how long the peer review record/file, including electronic records, should be retained. ☒

Check the box when item is completed

c. A location for the completed peer review record/file has been identified, and provisions have been made to retain electronic records associated with the work product and peer review. ☒
(Note: This can be the same location and provisions as identified in #4e.)
Location of Record/File: Superfund Records Center
Provisions for Electronic Records: Superfund Records Center and James Chapman

d. Someone has been assigned the responsibility for maintaining the record/file and electronic records, and ensuring that they are either archived or destroyed appropriately. *(Note: This can be the same person as identified in #4a.)* ☒
Contact Name and Phone No: James Chapman, 6-7195
Organization: SFD

16. Closeout of Checklist:

a. Items #1-15 of checklist have been completed. ☒

Signature of Peer Review Leader and Date Signed

James Chapman 3/21/03

b. A copy of the completed checklist has been given to the Div/Off Peer Review Coordinator. ☒

Signature of Div/Off Peer Review Coordinator and Date Signed

Steve Ostrodo 3/20/03

c. The completed checklist has been included in official peer review record/file. ☒

d. The work product has been moved from Peer Review Work Product List B to List A in the National Peer Review Database. ☐
Date Product moved to List A:
Will be completed during the week of March 24, 2003. The Peer Review data base is currently not available for data input.

SUPERFUND DIVISION
REMEDIAL RESPONSE BRANCH #1
SECTION #1

Site Name: Allied Paper/Portage Creek/Kalamazoo River Superfund Site

Type of Document: Transmittal of Peer Review Checklist #2 and the Peer Review Record for Avian and Mink PCB Toxicity Reference Values (TRV) [retitled: Toxicity Reference Values (TRVs) for Mammals and Birds Based on Selected Aroclors]

	INITIAL/DATE
James Chapman, Peer Review Leader	3/12/03
Shari Kolak, RPM	3/12/03
Tom Short, Section Chief	3/13/03
Wendy Carney, Branch Chief	3/13/03
William E. Muno, Division Director	WEM 3/17/03
Stephen Ostrodka, Division Peer Review Coordinator	SO 3/20/03

Return To: James Chapman (6-7195) or Shari Kolak (6-6151)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 5

DATE: August 22, 2002

SUBJECT: Transmittal of Peer Review Checklist #1 for the Allied Paper/Portage Creek/Kalamazoo River Superfund Site in Michigan

FROM: Shari Kolak, RPM

TO: Bill Muno, SFD Director

Attached to this memorandum is the Peer Review Checklist #1 for the Allied Paper/Portage Creek/Kalamazoo River Superfund Site in Michigan. The purpose of the checklist is to determine whether a scientific or technical work product needs peer review. More specifically, whether peer review is necessary for the derivation of wildlife PCB toxicity reference values (TRVs) from exposure-response curves (Edx) instead of a NOAEL-LOAEL approach.

This checklist has been prepared in accordance with the U.S. EPA Science Policy Council Peer Review Handbook and the October 2000 Region 5 Order entitled "Improved Policies and Procedures: Peer Review, Records Management, and Work Product Authorization of Scientific and Technical Work Products."

8/23/02

Peer Review Requested
WEM
8/13/02

Peer Review Checklist #1 -- Determining Whether a Work Product Needs Peer Review

Instructions: This checklist is based on the Agency's January 1998 Peer Review Handbook (EPA 100-B-98-001) and the October 2000 Region 5 Order "U.S. EPA Region 5 Improved Policies and Procedures: Peer Review, Records Management, and Work Product Authorization of Scientific and Technical Work Products" which constitute Region 5's standard operating procedures for peer review. If you have any questions about peer review or need clarification when completing this checklist, please refer to the Handbook, available via the internet at http://www.epa.gov/ord/spc/2peerrev.htm. Figure 1 on page 2 of the Handbook includes a useful flow chart and cross references to specific sections of the Handbook that are applicable to this checklist. You are also encouraged to consult with your Division or Office Peer Review Coordinator. The Division/Office Peer Review Coordinators will periodically request information from this checklist in order to update the National Peer Review Database.

1. **Title of Work Product:** Avian and Mink PCB Toxicity Reference Values (TRV)

2. **Product Description:** Derivation of PCB TRVs from exposure- or dose-response curves through an EDx procedure (Effective Dose, x - effect level of concern).

3. **Project Manager:** Shari Kolak, RPM, SFD, 6-6151
James Chapman, Ecologist, SFD, 6-7195
Name, Organization and Phone Number

4. **Determination if Work Product is Scientific or Technical:** *Please circle the appropriate answer*

a. Is the work product a scientific, engineering, economic, social science, or statistical document? *(Examples of such documents include: risk assessments, technical studies and guidance, analytical methods, scientific database designs, technical models, technical protocols, statistical surveys/studies, technical background materials, and research plans and strategies.)*	yes	no
b. Is the work product a scientific or technical document resulting from a grant, contract or cooperative agreement?	yes	no
c. Will the work product be used to support a research agenda, regulatory program, policy position, or other Agency position or action?	yes	no

If you answered "no" to all of these questions, your work product is not subject to EPA's peer review policy for scientific or technical work products and does not need to be placed on any of the peer review lists. Please proceed to #7 of this checklist. If you answered "yes" to any of these questions, your work product might need peer review; please continue on to #5 of this checklist.

5. **Determination if Work Product is a Major Work Product:**
Determination of whether a work product is "major" will largely be on a case-by-case basis. ***As the continuum of work products covers the range from the obviously major to those products that clearly don't need peer review (see Handbook, Section 2.2.3), there is no one single, easy yes/no answer to the test of "major".*** There also is no single definition of "significant." Determination of "major" and "significant" are the responsibility of the Division or Office Director who is the official Decision-Maker.

	Please circle the appropriate answer	
a. Does the work product establish a significant precedent, model, or methodology?	yes	no
b. Does the work product address significant controversial issues?	yes	no
c. Does the work product focus on significant emerging or "cutting edge" issues?	yes	no
d. Does the work product have significant cross-Agency or inter-agency implications?	yes	no
e. Does the work product involve a significant investment of agency resources?	yes	no
f. Does the work product consider an innovative approach or application for a previously defined problem, process or methodology?	yes	no
g. Is the work product required to be peer reviewed by statute or other legal mandate?	yes	no
h. Does the work product support a regulatory decision, policy or guidance of major impact? *(Major impact can mean that it will have applicability to a broad spectrum of regulated entities and other stakeholders, or that it will have narrower applicability, but with significant consequences on a smaller geographic or practical scale.)*	yes	no
i. Is the work product an application of or modification to an existing, adequately peer reviewed methodology or model that departs significantly from the situation it was originally designed to address?	yes	no

If you answered "yes" to any of these questions, your work product needs peer review unless special circumstances exist; please continue on to #6. If you answered "no" to all of these questions, your work product probably does not need peer review. However, peer review can always be done to improve the quality of the work product. Please proceed to #7 of this checklist.

6. **Determination Whether Circumstances Exist Where a Major Work Product Would Not Be Peer Reviewed:**

	Please circle the appropriate answer	
a. Was the work product previously reviewed by recognized experts or an expert body? (*Note: Peer review of an EPA work product by a recognized refereed journal strengthens the scientific credibility of the work product but does not eliminate the need to have the work product itself peer reviewed for issues and concerns to support an Agency action. See Sections 2.4.4 and 2.4.5 of the Handbook for more details.)*	yes	no
b. Are the scientific or technical methodologies or information being used commonly accepted in the field of expertise?	yes	no
c. Has the regulatory activity or action which the work product supports been terminated or canceled?	yes	no
d. Is there a statutory or court ordered deadline, or a time constraint which may limit or preclude peer review of the work product?	yes	no

If you answered "yes" to any of these questions, your work product probably does not require peer review. This decision with the justification needs to be concurred with and signed off by the Division/Office Director. The decision with the justification must be retained in the peer review files and noted in Peer Review Work Product List C in the National Peer Review Database. Continue on to #7. If you answered "no" to all of these questions, proceed to #8.

7. **Next Steps For Work Products That Will Not Be Peer Reviewed:**

d. Division/Office Director concurs with the decision that the work product should not be peer reviewed.

Despite the yes in item 6(b), this product needs to be peer reviewed.

_____
Signature of Division/Office Director and Date Signed

e. A copy of this completed checklist has been given to the Div/Off Peer Review Coordinator and put in the official peer review files in the Division/Office.

_____
Signature of Div/Off Peer Review Coordinator and Date Signed

_____
Location of Div/Off Peer Review Files

f. Work product has been placed on Peer Review Work Product List C in the National Peer Review Database. *(Note: This only applies to those work products subject to the peer review policy.)*

Signature of Div/Off Peer Review Coordinator and Date Signed

If all of the necessary information is complete, you are done. You don't need to proceed any further with this checklist.

8. **Next Steps For Work Products That Will Be Peer Reviewed:**

g. Division/Office Director has been consulted and concurs with the decision that the product should be peer reviewed.

W. E. Mann 8/23/02
Signature of Division/Office Director and Date Signed

h. A copy of this completed checklist has been given to the Division/Office Peer Review Coordinator and put in the official peer review files in the Division/Office.

Steve Estrada 8/29/02
Signature of Div/Off Peer Review Coordinator and Date Signed

7th floor record center
Location of Div/Off Peer Review Files

c. Work product has been placed on Peer Review Work Product List B in the National Peer Review Database.

Steve Estrada 8/29/02
Signature of Div/Off Peer Review Coordinator and Date Signed

Because your work product will be peer reviewed, you need to complete a second checklist entitled "***Peer Review Checklist #2 -- Conducting a Peer Review.***"

SUPERFUND DIVISION

REMEDIAL RESPONSE BRANCH #1

SECTION #3

Site Name: Allied Paper/Portage Creek/Kalamazoo River Superfund Site

Type of Document: Transmittal of Peer Review Checklist #1 for the Allied Paper/Portage Creek/Kalamazoo River Superfund Site

	INITIAL/DATE
Shari Kolak, RPM:	for S.K. 8/23/02
Matthew Mankowski, Acting Section Chief:	8/23/02
Wendy L. Carney, Chief:	8/23/02
Bill E. Muno, Division Director:	VBM 8/29/02
Stan Ostrodka	8/29/02

Return To: Shari Kolak (6-6151) or Lorraine Navarrete (3-6425)

Peer Review Charge for Mink and Chicken PCB Toxicity Reference Values Derived Through an EDx (effective dose) Procedure

Background

Continuing Need for Aroclor-based TRVs

Although congener-specific analyses are recommended for assessing risks to PCBs, Aroclor-based toxicity reference values (TRVs) are still needed for several reasons. 1) The PCB database at many sites is predominantly or solely Aroclor data. This is especially true of historic data. 2) At contentious sites, the lengthy process for resolving disagreements has resulted in a need to finalize Aroclor-based risk assessments initiated prior to the current emphasis on congener-based approaches. In these situations, abandonment of the an Aroclor approach will entail substantial delay and cost for resampling media and biota to provide synoptic congener data. 3) There is a larger database available on the ecotoxicological effects of PCBs on an Aroclor basis as compared to a dioxin toxic equivalent (TEQ) basis. 4) The utility of the TEQ-based ecotoxicological studies is also compromised by the use of inconsistent toxic equivalency factors (TEF). Conversion to a common TEQ basis is feasible only if the original congener data is reported so that the TEF scheme of choice can be applied, but the underlying congener data are rarely reported in journal articles–further reducing the pool of useable TEQ studies. Studies based on bioassay TEQs, such as the H1I4E rat hepatoma cell line, cannot be directly compared to calculated TEQs, and the bioassay results vary with the choice of solvent for dosing the cells. 5) The key premise of the TEQ approach is that the effects of PCBs are primarily due to aryl hydrocarbon receptor (AhR)-mediated processes (dioxin-like effects). Although AhR-mediated effects are frequently reported to be more sensitive endpoints compared to non-AhR effects, it is not clear how generally this relationship applies across taxa and endpoints. In the absence of a non-AhR TEF scheme, an Aroclor-based assessment can provide an indication whether significant non-AhR effects may have been missed in a TEQ-based assessment.

One of the criticisms of Aroclor-based assessments is that the results are more variable compared to TEQ-based assessments. However, in one such comparison by Leonards, et al. (1995), no distinction was made between different Aroclors or Clophens (total PCB vs. reproductive effects in mink was unfavorably compared to TEQ vs. reproductive effects). This comparison was biased since different Aroclors or Clophens differ in their toxicity.

NOAEL/LOAEL Approach

A widely used approach for determining TRVs depends on two statistically-based thresholds: the no observed adverse effect level (NOAEL), which is the highest dose tested that did not result in a statistically discernible effect compared to the control, and the lowest observed adverse effect level (LOAEL), which is the lowest dose that resulted in a statistically discernible adverse effect. Shortcomings in this approach have been long recognized–the main one is that the NOAEL and LOAEL are affected by factors unrelated to toxicity. An obvious factor is that the TRVs can only be selected from the particular doses used in an experiment (commonly the tested doses are an

order of magnitude apart so there are large gaps in the data). Second, statistical significance is not solely determined by toxicity, but also by the statistical power of the study. This has two implications: 1) studies performed with low statistical power will result in higher TRVs compared with studies with high statistical power for the same chemical and receptor, and 2) since the TRVs are statistically defined, the level of adverse effects associated with the NOAEL or LOAEL varies greatly between studies (for example, statistically-derived NOAELs may be associated with adverse effects in as much as 50 % of the test organisms). A related consideration is that this approach acts as a disincentive for improving the quality and statistical power of industry-funded toxicological testing since less rigorous studies are less expensive and have low statistical power that results in higher and less protective TRVs.

EDx or ECx Approach

An alternative is to use the data from toxicological studies to develop dose- or exposure-response relationships, and to use the relationships to determine the no-effect and low-effect doses or exposures that correspond to selected effect levels. This frees the analysis from the specific doses used in a study (a TRV can now be interpolated between the tested doses), and from the non-conservative bias of tests with inadequate statistical power. This approach is referred to as EDx or ECx (effective dose or concentration; x represents the selected effect level of concern).

An example of the ECx approach is in the recommended procedure for analyzing the results of effluent toxicity testing in the USEPA water program (the low effect concentration is defined as the EC_{75}, that is, the concentration that corresponds to a 25 % decrement in response compared to controls).

Work Product

The TRVs for Aroclors have been revisited in Region 5 for application in Superfund sites in which congener data is not available, and for supplemental use to accompany TEQ-based assessments in sites with congener data. Recently, derivation of Aroclor-based TRVs by taking the geometric means of no or lowest observed adverse effect levels (NOAEL or LOAEL), respectively, from selected studies was challenged for including studies with field-contaminated prey that may be confounded by the effects of co-contaminants. The work products under review are the result of combined analysis of studies that reported the reproductive effects of feeding commercial PCB products to mink and chicken.

The effluent toxicity testing guidance in the water program (e.g., Klemm, et al. 1994; Chapman, et al. 1995) was modified for deriving PCB TRVs from multiple chicken and mink studies. 1) The results of the various studies were normalized so they could be compared on a common basis (the guidance is written for interpreting the results of a single experiment in contrast to the multiple mink or chicken studies performed by different researchers that are analyzed for the PCB TRVs). The normalization was accomplished by dividing each mean treatment response by the respective mean control response. The resulting relative responses are plotted on semi-log graphs (log dose or concentration vs. relative response). The plots showing interpretable dose-

response relationships are used to derive the no- and low-effect TRVs by a linear interpolation between the treatments that bracket the effect level of concern. 2) Interpolation is only performed when the effect level of concern falls within the linear portion of the dose-response plot (to avoid uncertain interpolations). 3) A log-linear interpolation is used since it gives a better fit within the linear portion of the data plots compared to the linear interpolation in the guidance. 4) Data are not adjusted when treatment responses exceed control responses (relative responses > 1), since the recommended procedure applies to the results of single, not multiple studies. 5) The procedure for deriving confidence intervals is not implemented since the only available data from the published mink and chicken studies are the treatment means (the underlying data for the individual replicates were not presented for any of the studies).

An alternate approach would be to fit curves to the data, and use the non-linear regressions to calculate the low-effect levels. This approach was not used because only the treatment and control mean responses are reported in the published literature. The underlying replicate data, which would provide the best basis for curve-fitting and are necessary for calculating confidence intervals, are not available.

An additional modification was made for the mink TRVs only. Three studies have shown dramatic increases in adverse effects following continuous exposure to PCBs over 2 breeding seasons or 2 generations of females compared with exposure in 1 breeding season. These studies used field-contaminated prey, or Clophen-supplemented feed, so the 2-season or 2-generation results cannot directly be used to interpolate 2-season or generation Aroclor TRVs. Instead, the 1-season Aroclor TRVs are multiplied by the mean ratio of the available 2-season or generation TRVs divided by the corresponding 1-season TRVs to derive Aroclor TRVs protective for sustained occupancy of a site by female mink.

Literature Cited

Chapman, G . D. Denton, and J. Lazorchak. 1995. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to West Coast Marine and Estuarine Organisms. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA/600/R-95-136.

Klemm, D., G. Morrison, T. Norberg-King, W. Peltier, and M. Heber. 1994. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms, 2nd ed. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA/600/4-91/003.

Leonards, P., T. de Vries, W. Minnaard, S. Stuijfzand, P. de Voogt, W. Cofino, N. van Straalen and B. van Hattum. 1995. Assessment of experimental data on PCB-induced reproduction inhibition in mink, based on an isomer- and congener-specific approach using 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalency. Environ Toxicol Chem 14: 639-652.

Peer Review Charge

The peer review charge is to evaluate the methodology for deriving Aroclor TRVs. The charge does not include review of the input data (although documentation of the data and the specific sources is included in the materials provided to reviewers), but the methodology for normalization of the data is part of the charge.

Charge Questions

Peer Reviewers should comment on the following:

1) Is the data normalization method (relative response = treatment response / control response) appropriate for combining the results of different toxicity studies into single dose- or exposure-response plots? If not, what would be a more appropriate method? Explain.

2) Is the linear interpolation method appropriate for deriving the dose or dietary concentration corresponding to selected effect levels? If not, what method would be more appropriate for use with mean data (when the underlying replicate data are not available)? Explain.

3) Are the effect levels appropriate (75 % relative response for low effect, 100 % relative response for no effect)? If not, what effect levels would be more appropriate. Explain.

4) Are the following modifications of the linear interpolation method recommended for effluent toxicity testing in the Water Program appropriate? If not, how should the method be applied? Explain.

a) Restricting interpolation to the linear portion of the data plots.

b) Use of log-linear interpolation in place of (arithmetic) linear interpolation.

c) No adjustment when treatment response exceed control responses (relative response allowed to exceed a value of 1.0).

d) No confidence interval estimation.

5) Regarding the mink TRVs only, is the procedure for adjusting the TRV based on exposure during a single breeding season to derive a TRV protective for continuous exposure through two breeding seasons or two generations of females appropriate? (The single-season Aroclor TRVs are adjusted by multiplying by the mean ratio of the 2-season or generation TRVs divided by 1-season TRVs from feeding studies with field-contaminated prey or Clophen A50.) If the procedure is not considered appropriate, are there any recommended alternative approaches? Explain.

6) Any other comments on the methodology? [optional]

Due Date

October 21, 2002

Format

Electronic submittal to chapman.james@epa.gov, WordPerfect is preferred, version 9 or lower. In case anyone want to submit a spreadsheet as part of the comments, Lotus123 is preferred, version 9.5 or lower for Windows.

Point of Contact

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JAMES CHAPMAN To: Tala Henry, Mark Sprenger, Glenn Suter, Dale Hoff, Chris Cubbison cc
10/02/2002 03:32 PM Subject: Peer Review Charge - 1

Thank you for your assistance.

I have attached the peer review charge (PCB EDx peer rev charge.wpd). In this message I have also attached several files related to the mink TRV. PCB mink TRV sum.wpd is the workproduct you are reviewing.

Although the peer review is for the methodology only, not the underlying data, I have attached several spreadsheets in case you want to check anything I did. PCB mink RR.123 documents the data sources and shows the relative response calculations. PCB mink graph file.123 is a translation of the SYSTAT file I used to generate the exposure-response plots. PCB mink linear interpol TRV2.123 shows the TRV calculation for both the log-linear approach I used in the memo, and the linear approach in the guidance.

I will be in the field the rest of this week, and will be on vacation the next week, returning to the office after Columbus Day. If anyone needs a copy of any of the papers I cited, please contact my supervisor Larry Schmitt (he has all the mink and chicken studies I used, the Leonards, et al. paper, and a copy of the linear interpolation section of the effluent testing guidance (I misplaced Klemms, et al., but he has a copy of Chapman, et al.).

Please contact Shari Kolak during my absence if there are scheduling issues.

I am sending a second message with the chicken files.

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PCB EDx PR charge.wpd


PCB mink TRV sum.wp


PCB mink linear interpol TRV2.1 (Table 1)


PCB mink RR.123 (Table 2)


PCB mink graph file.123

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 5

DATE: September 24, 2002

SUBJECT: Draft Mink PCB Toxicity Reference Value (TRV)

FROM: James Chapman, Ph.D., Ecologist

TO: Shari Kolak, RPM

Recommended Mink PCB Toxicity Reference Values

The recommended dietary PCB low-effect TRV for mink is 0.6 mg/kg wet weight, based on the effects of A1254 on the number of live kits per mated female and kit bodyweight, adjusted for continuous exposure through two breeding seasons or generations. The no-effect TRV cannot be reliably interpolated, but is greater than 0.02 mg/kg (control dietary concentration). Since there is a narrow range between no-effect and low-effect TRVs for A1242 and Clophen A50 (see below), the A1254 no-effect TRV is unlikely to be less than one-half of the low-effect TRV, for an estimated no-effect value of 0.3 mg/kg.

Although kit survival appears to be a more sensitive endpoint compared to live kit production or kit bodyweight, the data are insufficient for determining kit survival TRVs for A1254, other than to state that the low-effect dietary concentration is less than 1 mg/kg for a single season of exposure, and would be even less for exposure through multiple seasons or generations.

Surprisingly, no mink feeding studies were located for A1248. However, A1248 is as potent as A1254 in mammalian bioassays (Tillitt, et al. 1992), so the A1254-based TRVs are applicable to A1248.

The dietary TRVs for A1242 are 1.3 to 1.4 mg/kg for live kit production (no effect to low effect), adjusted for two-season or two-generation exposure. Data are insufficient for other endpoints.

The dietary TRVs for Clophen A50 over 2 seasons exposure are 1.0 to 1.3 mg/kg for live kit production (no effect to low effect), 2.3 mg/kg for kit bodyweight (low effect), and less than 0.8 mg/kg for kit survival (low effect).

TRVs calculated from exposure to commercial PCB products may underestimate the toxicity of PCBs in the field because of weathering and selective retention in biota.

Method Summary

An issue raised concerning the Baseline Ecological Risk Assessment for the Allied Paper, Inc./Portage Creek/Kalamazoo River Superfund site is the appropriate toxicity reference value (TRV) for PCBs in mink. This memo presents an analysis of the effects of PCBs on mink.

TRVs are derived from exposure-response curves by interpolation of the effective dietary concentration (EC_x) to female mink that corresponds to specific relative responses (calculated as the treatment response divided by the control response). The low-effect level is defined as 0.75 of the control response for any toxicological endpoint (EC_{75}), and the no-effect level as equal to the control response (EC_{100}) (or the treatment response closest to the EC_{100} if interpolation is infeasible).

Two studies performed with field-contaminated prey, and one with Clophen A50, reported the reproductive effects of PCBs associated with exposures over both one and two breeding seasons, and one of the field studies also reported the reproductive effects in two generations of exposed females. All of these studies showed increased adverse effects in the second year or generation of continuous exposure. Since only single-season exposures have been reported for commercial Aroclor feeding studies, TRVs protective for long-term occupancy of a site by female mink are calculated by multiplying the single-season TRVs by the mean ratio of the response to 2 breeding seasons or generations exposure divided by the response to a single season exposure.

Methods

Study results are selected according to the following criteria: 1) studies published in journals (gray literature excluded), 2) matched control and treatment responses, 3) continuous PCB exposure (responses following cessation of exposure are excluded), and 4) treatment responses individually reported (responses based on combinations of exposure levels or different Aroclor treatments are excluded). Statistical significance is not a criterion for selection since the objective is to develop dose- or exposure-response relationships over the full gradient tested. When response data are reported for more than one exposure time, data for later exposure periods take precedence over earlier exposure periods or data averaged over the entire exposure period. Data are taken from text, tables, or figures so long as the selection criteria are met.

Two exceptions are made for the study selection. Käkelä, et al. (2002) exposed mink to A1242-supplemented food for 21 weeks, but then switched to the control diet at the onset of breeding. This treatment is included because there was no delay between the cessation of A1242 exposure and initiation of breeding, therefore depuration [1] did not occur prior to breeding. Although effects might be underestimated due to depuration during the breeding period, this does not appear to be the case. The sole TRV calculation involving this treatment is for live kits per mated female for A1242, in which the Käkelä, et al. (2002) datum is consistent with other study results (see Figure 2). The other exception involves a field-exposure study, which is not used in the TRV calculations. Platanow and Karstad (1973) feed A1254 to cows, and then fed meat from the exposed cows to mink. The sole control response reported was the number of live kits per mated female. Other responses are included only when the treatment response was zero (e.g., 0 kit survival in the 0.64 ppm treatment), because the relative response in this case is not affected by the value of the control response [2].

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[1] Depuration is the elimination of chemicals from an animal after the cessation of exposure, through metabolic conversion and/or excretion.

[2] Relative response (RR) = treatment response / control response. When the treatment response = 0, RR = 0 for all positive values of the control response.

TRVs are derived from feeding studies in which commercial PCB products were added to the mink diet. Studies with field-contaminated prey are not used for TRV derivation, but are relied on in part for evaluating the effect of continuous exposure through 2 breeding seasons or generations compared to exposure in a single season.

Treatment responses are normalized relative to the respective control responses (relative response = treatment response / control response) so that multiple studies may be compared on a common basis (for example, Leonards, et al. 1995) (Table 2). TRVs are defined in terms of percent response relative to control: 100 % is the no-effect level (EC_{100}), and 75 % is the low-effect level (EC_{75}), where EC_x is the effective concentration resulting in a response that is X % of the control response. The EC_{75} is an alternative to the lowest observed adverse effect concentration (LOAEC)[3]. The EC_{75} is derived from the dose-response curves by a log-linear interpolation between the responses that bracket the 75 % effect level, a modification of the linear interpolation method used for estimating the chronic toxicity of effluents[4] (Klemm, et al. 1994). Interpolation is performed only when the target value falls within the linear portion of the exposure response plots. No-effect levels are either taken directly from the data if the treatment response does not exceed the control response (but has a relative response >0.9), or is interpolated for the EC_{100} if the treatment response exceeds the control response (relative response > 1.0). Exposure concentrations or effects are not extrapolated beyond the existing data ranges.

Curve-fitting is not done because each of the data points represents a mean response. The best database for curve-fitting is the underlying replicate data of the various studies, which are not available in the publications.

The results of mink studies are plotted below. Exposure-response relationships are evident for number of live kits per mated female (Figures 2, 3, and 7-9), kit bodyweight (Figures 5, 10-12, and 17), and kit survival (Figures 13-15 and 18). Data were also normalized for whelping frequency, total kits per whelped female, and live kits per whelped female (Table 2), but these effects are integrated in the live kits per mated female endpoint, so are not separately analyzed.

The interpolated TRVs are given in Table 1. The dietary TRVs (mg/kg ww) for exposure in a single breeding season are as follows: A1242–2.4 to 2.7 (no to low effect, respectively) for live kits per mated female; A1254–1.1 (low effect) for live kits per mated female and kit bodyweight; and Clophen A50–1.8 to 3.1 (no to low effect) for live kits per mated female. The no effect levels for A1254 cannot be interpolated because they are outside the linear portion of the data plots, but are greater than 0.02 and less than 1.0 mg/kg ww.

The A1254 relative response for kit survival appears to show a no effect level of 1.0 mg/kg ww (Wren, et al. 1987) and complete mortality at 2.0 mg/kg ww (Aulerich and Ringer 1977) (Figure 6). Although Wren, et al. (1987)

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[3] The difference between a LOAEC and an EC_{75} is that the former is based on a statistically discernible difference between treatment and control responses, regardless of the amount of the effect, while the latter is based on a specified effect level (75 % response compared to controls) interpolated from an exposure-response plot (dietary concentration vs. response).

[4] One modification is that the interpolation is performed with the base 10 logarithm of the dose or concentration. This is done because most of the responses are linear against the logarithm of the dose or egg concentration (see figures). Another modification is that no adjustment is made when treatment responses exceed control responses, since the recommended procedure applies to the results of a single study, not the multiple studies used here. Note that there are errors in the Appendix L example calculation in Klemm, et al. (1994).

show the same kit survival for controls and the 1 mg/kg treatment, they reported a dramatic shift in the cause of the mortality in the two groups–mainly trauma and infection in the control kits (9 of 12 kits that died after birth), but predominantly starvation in the treatment kits (13 of 14 treatment kits that died after birth). Since none of the control kit mortality was due to starvation, and wasting syndrome is a well-characterized effect of chemicals with dioxin-like effects (including PCBs), the 1 mg/kg treatment cannot be considered the no effect dietary concentration for kit survival. This means that the low effect dietary A1254 TRV for kit survival is less than 1 mg/kg ww, and the no effect TRV is greater than 0.02 mg/kg ww, but more precise determinations cannot be made with the existing data.

Two studies performed with field-contaminated prey (Hornshaw, et al. 1983; Restum, et al. 1998), and one with Clophen A50 (Brunström, et al. 2001), reported the reproductive effects of PCBs associated with exposures over both one and two breeding seasons. Restum, et al., also reported the reproductive effects in two generations of exposed females. All of these studies showed increased adverse effects in the second year or generation of continuous exposure compared to the first (Figures 7-12 and 14-15). For example, in the study by Hornshaw, et al., the number of live kits per mated female was 66 to 79 % of the control value at 0.63 to 0.69 ppm PCB for exposure over a single breeding season, but decreased to only 11 % of the control value at 0.66 ppm PCB for exposure over two breeding seasons (Figure 8). Kit survival in the same treatments decreased from 65 to 73 % of the control value for single-season exposure to 0 survival for exposure over two breeding seasons (Figure 14). Kit bodyweight was also affected (Figure 11). Hornshaw, et al. had only a single 2-season exposure treatment, so TRV interpolation is precluded from this study, but TRV comparisons are possible for the other two studies.

Brunström, et al. (2001) fed mink diets spiked with Clophen A50, one of the European commercial PCB products, and reported results for both 1 and 2 years of exposure. Sufficient data are available to calculate TRVs for both exposure periods for the number of live kits per mated female (Table 1 and Figure 7). The low effect TRV for exposure over 2 breeding seasons (1.3 ppm PCB) is 42 % of the corresponding TRV for 1 season exposure (3.1 ppm), and the 2-season no effect TRV (1.0 ppm) is 58 % of the 1-season value (1.8 ppm).

Restum, et al. (1998) fed mink various proportions of field-contaminated carp from Saginaw Bay, Michigan, and reported results for single and multiple years and generations of exposure (Figures 9, 12, and 15). Six comparisons are shown in Table 1 between 1-season and 2-season or 2-generation TRVs for live kits per mated female, kit bodyweight, and kit survival. Note that for live kits per mated female, the ratios of 2-season or 2-generation responses divided by the 1-season response result in maximum ratios. This is because the 1-season live kit per mated female TRV cannot be interpolated (it is at a higher dietary concentration than the highest tested). Instead of making an uncertain extrapolation, the relative response at the highest dietary concentration tested is used for the 1-season low effect TRV (0.9 relative response at 1.0 ppm PCB). Since the 1-season EC_{75} is at a dietary concentration greater than 1 ppm, the actual product of dividing the 2-season or 2-generation TRVs by the 1-season TRV would be smaller than the ratios shown in Table 1 for live kit per mated female (0.39 and 0.28, respectively). There are no such issues for the other endpoints. Overall, the ratio of 2-season or 2-generation TRVs divided by 1-season TRVs ranges from <0.28 to 0.87 for the various endpoints in the Restum, et al., study (Table 1).

For the purposes of adjusting the single-season Aroclor TRVs so they will be protective for sustainable occupancy by mink for multiple years or generations at a given location, the 1-season TRVs are multiplied by the mean ratio of the 2-season or 2-generation low effect TRVs divided by the 1-season TRVs based on the studies by Brunström, et

al. (2001) and Restum, et al. (1998). The mean ratio of the seven comparisons is 0.52, that is, on average, the low effect TRV for 2-seasons or 2-generations exposure is 52 % of the low effect TRV for 1-season exposure to PCBs. Accordingly, the single-season TRVs for A1242 and A1254 are multiplied by 0.52 to derive TRVs for long-term sustainability. By this approach, the A1254 low effect TRV is 0.6 mg PCB/kg diet for live kits per mated female and kit bodyweight, and the A1242 no and low effect TRVs are 1.3 to 1.4 mg/kg for live kit production.

TRVs may be assessed for two additional endpoints for exposure over 2 breeding seasons to A50–2.3 mg/kg for kit bodyweight (low effect) and less than 0.8 mg/kg for kit survival (low effect) (Table 2). Kit survival was not reported for 1 season exposure to A50, and the single-season TRV for kit bodyweight cannot be interpolated from the data (greater than the highest dietary concentration tested).

The original data used for calculating relative responses and their sources are documented in a separate spreadsheet titled "Summary of Mink PCB Studies and Relative Responses" (PCB mink RR.123).

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Brunström, B., B. Lund, A. Bergman, L. Asplund, I. Athanassiadis, M. Athanasiadou, S. Jensen, and J. Örberg. 2001. Reproductive toxicity in mink (*Mustela vison*) chronically exposed to environmentally relevant polychlorinated biphenyl concentrations. Environ Toxicol Chem 20: 2318-2327.

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Käkelä, A., R. Käkelä, H. Hyvärinen, and J. Asikainen. 2002. Vitamins A_1 and A_2 in hepatic tissue and subcellular fractions in mink feeding on fish-based diets and exposed to Aroclor 1242. Environ Toxicol Chem 21: 397-403.

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Leonards, P., T. de Vries, W. Minnaard, S. Stuijfzand, P. de Voogt, W. Cofino, N. van Straalen and B. van Hattum. 1995. Assessment of experimental data on PCB-induced reproduction inhibition in mink, based on an isomer- and congener-specific approach using 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalency. Environ Toxicol Chem 14: 639-652.

Platonow, N. and L. Karstad. 1973. Dietary effects of polychlorinated biphenyls on mink. Can J Comp Med 37: 391-400.

Restum, J., S. Bursian, J. Giesy, J. Render, W. Helferich, E. Shipp, D. Verbrugge, and R. Aulerich. 1998. Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron,

on mink: 1. Effects on mink reproduction, kit growth, and survival, and selected biological parameters. J Toxicol Environ Health Part A 54: 343-375

Tillitt, D., G. Ankley, J. Giesy, J. Ludwig, H. Kurita-Matsuba, D. Weseloh, P. Ross, C. Bishop, L. Sileo, K. Stromborg, J. Larson, and T. Kubiak. 1992. Polychlorinated biphenyl residues and egg mortality in double-crested cormorants from the Great Lakes. Environ Toxicol Chem 11: 1281-1288.

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John Giesy, Michigan State University, Entrix
Alan Blankensip, Entrix

Figure 1. Live Kits, Commercial Product, Exposed 1 Breeding Season

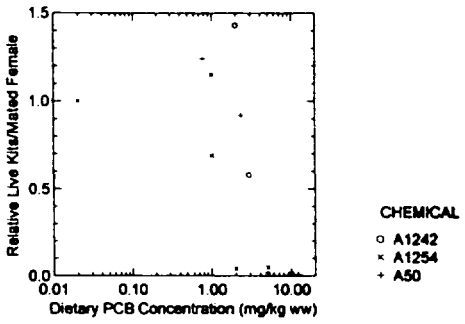


Figure 2. Live Kits, A1242, Exposed 1 Season

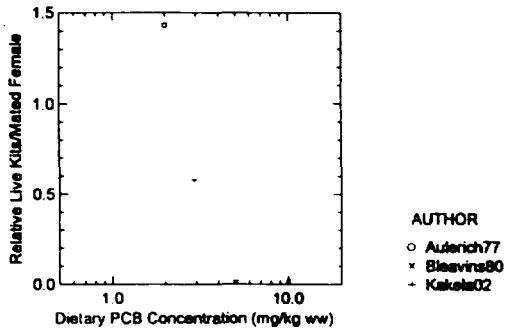


Figure 3. Live Kits, A1254, Exposed 1 Season

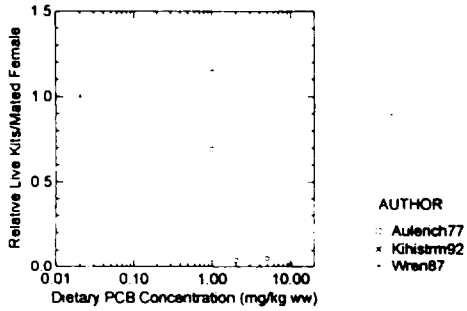
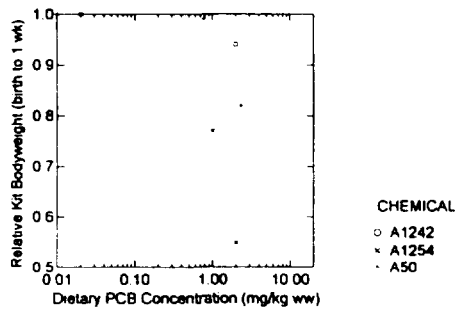


Figure 4. Kit Bodyweight, Product, Exposed 1 Season



Author is lead author and date. See notes to Table 2 for citations.

Figure 5. Kit Bodyweight, A1254, Exposed 1 Season

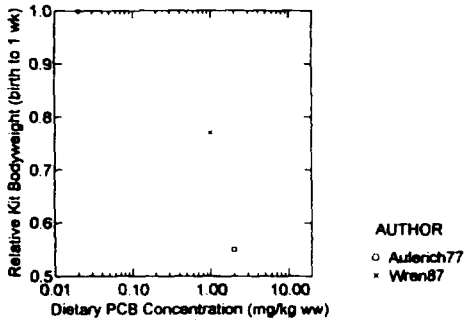


Figure 6. Kit Survival, A1254, Exposed 1 Season

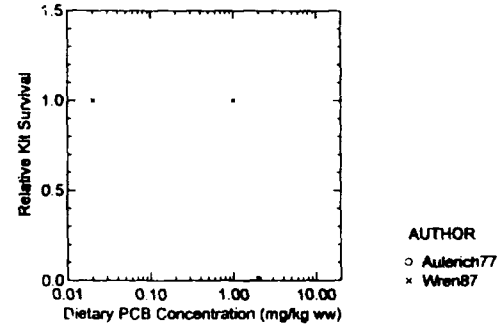


Figure 7. Live Kit, A50, Exposed Multiple Seasons

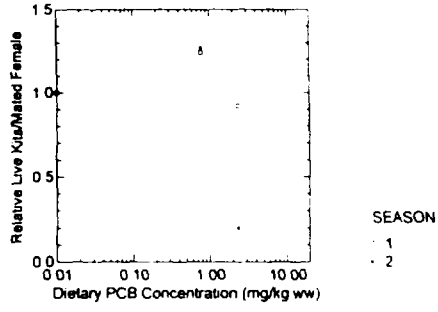


Figure 8. Live Kit, Field, Exposed Multiple Seasons, Hornshw83

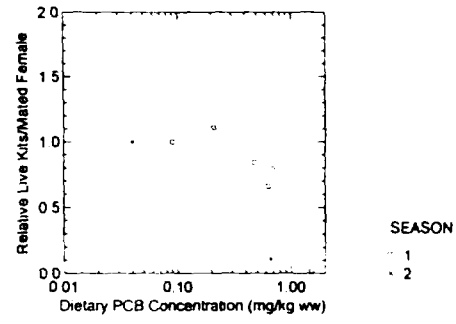


Figure 9. Live Kit, Field, Exposed Multiple Season and Generation, Restum98

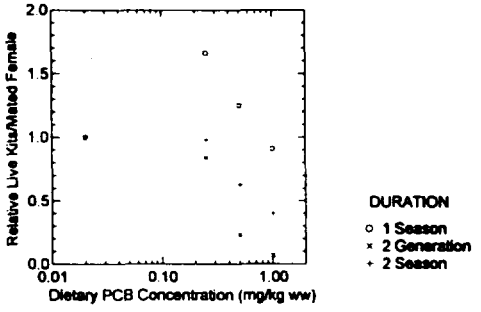


Figure 10. Kit Bodyweight, A50, Exposed Multiple Season and Generation, Restum98

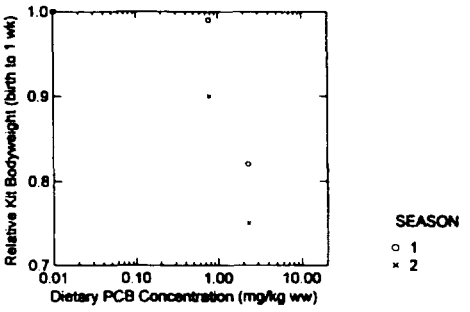


Figure 11. Kit Bodyweight, Field, Exposed Multiple Season, Hornshw83

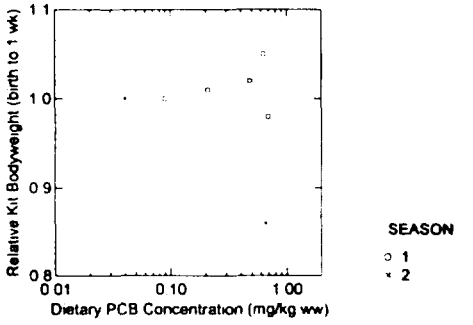


Figure 12. Kit Bodyweight, Field, Exposed Multiple Season and Generation, Restum98

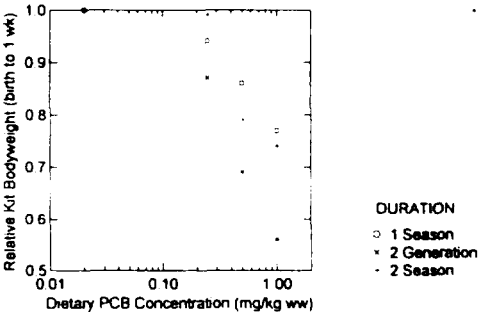


Figure 13. Kit Survival, A50, Exposed 2 Season

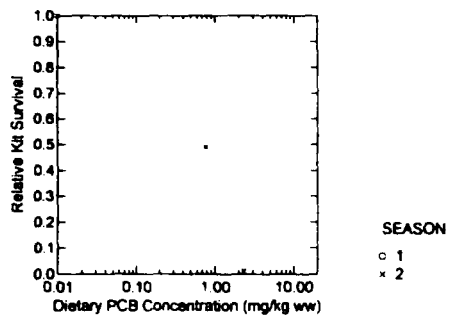


Figure 14. Kit Survival, Field, Exposed Multiple Season, Hornshw83

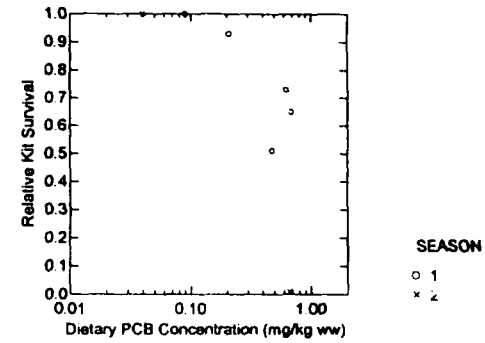


Figure 15. Kit Survival, Field, Exposed Multiple Season and Generation, Restum98

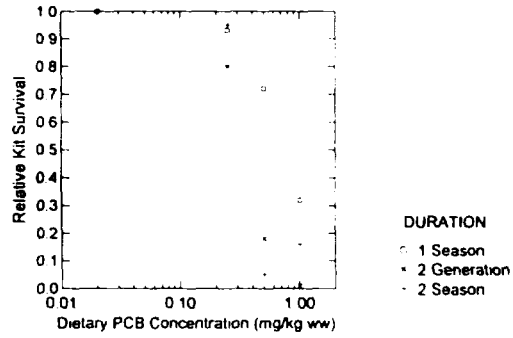


Figure 16. Live Kit, Field, Exposed 1 Season

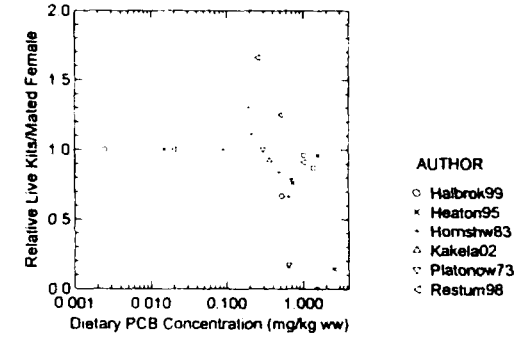


Figure 17. Kit Bodyweight, Field, Exposed 1 Season

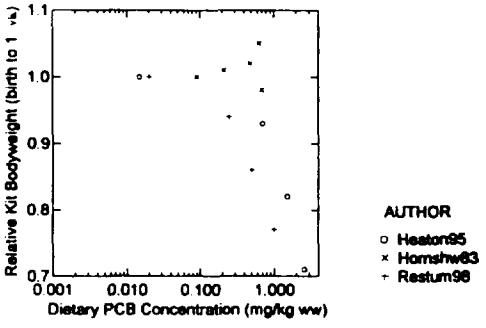


Figure 18. Kit Survival, Field, Exposed 1 Season

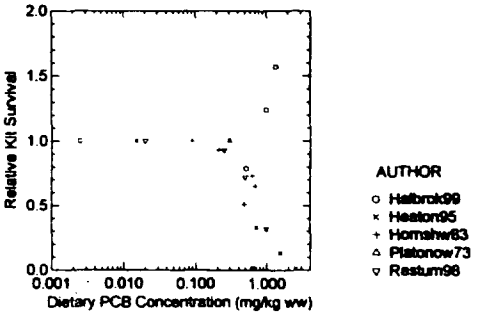


Table 1. Log-Linear Interpolation of PCB Toxicity Reference Values (TRV) for Mink

Chem. or Field study author	Response	Exposure Duration	Control RR	Treatment conc < TRV conc	Treatment conc < TRV RR	Treatment conc > TRV conc	Treatment conc > TRV RR	Target RR	P	TRV	Effect level	Study
			M_i	C_i	M_i	C_{i+1}	M_{i+1}					
Commercial PCB feeding studies (mg PCB/kg diet, ww)												
A1242	live kit/ mated ♀	1 season	1	2	1.43	2.88	0.58	0.75		2.68	low effect	Aulerich77, Kakela02
			1	2	1.43	2.88	0.58	1		2.41	no effect	Aulerich77, Kakela02
A1254	live kit/ mated ♀	1 season	1	1	0.92	2	0.04	0.75		1.14	low effect	Wren87, Aulerich77
			1			1	0.92	1		<1.00	no effect	Wren87, Aulerich77
A1254	kit bodywt	1 season	1	1	0.77	2	0.55	0.75		1.07	low effect	Wren87, Aulerich77
			1	0.02	1			1		>0.02	no effect	Wren87
A1254	kit survival	1 season	1	0.02	1	2	0	0.75		<1.00	low effect	Wren87, Aulerich77
			1	0.02	1			1		>0.02	no effect	Wren87
A50	kit bodywt	2 season	1	0.77	0.9	2.31	0.75	0.75		2.31	low effect	Brunstm01
			1	0.01	1			1		>0.01	no effect	Brunstm01
A50	kit survival	2 season	1			0.77	0.49	0.75		<0.77	low effect	Brunstm01
			1	0.01	1			1		>0.01	no effect	Brunstm01
Comparison of 1 breeding season exposure vs 2 breeding seasons or generations continuous exposure												
A50	live kit/ mated ♀	1 season	1	2.31	0.92	12	0	0.75		3.13	low effect	Brunstm01, Khistrm92
		1 season	1	0.77	1.24	2.31	0.92	1		1.76	no effect	Brunstm01
		2 season	1	0.77	1.27	2.31	0.2	0.75		1.31	low effect	Brunstm01
		2 season	1	0.77	1.27	2.31	0.2	1		1.02	no effect	Brunstm01
Ratio 2 season / 1 season			*0.58 no effect*									
Ratio 2 season / 1 season			*0.42 low effect*									
Restum	live kit/ mated ♀	1 season	1	1	0.91			0.75		>1.00	low effect	Restum98
		2 season	1	0.25	0.98	0.5	0.63	0.75		0.39	low effect	Restum98
		2 generation	1	0.25	0.84	0.5	0.23	0.75		0.28	low effect	Restum98
Ratio 2 season / 1 season			*<0.39 low effect*									
Ratio 2 generation / 1 season			*<0.28 low effect*									
Restum	kit bodywt	1 season	1	1	0.77			0.75		1.00	low effect	Restum98
		2 season	1	0.5	0.79	1	0.74	0.75		0.87	low effect	Restum98
		2 generation	1	0.25	0.87	0.5	0.69	0.75		0.40	low effect	Restum98
Ratio 2 season / 1 season			*0.87 low effect*									
Ratio 2 generation / 1 season			*0.40 low effect*									
Restum	kit survival	1 season	1	0.25	0.93	0.5	0.72	0.75		0.45	low effect	Restum98
		2 season	1	0.25	0.95	0.75	0.11	0.75		0.32	low effect	Restum98
		2 generation	1	0.25	0.8	0.5	0.18	0.75		0.26	low effect	Restum98
Ratio 2 season / 1 season			*0.72 low effect*									
Ratio 2 generation / 1 season			*0.58 low effect*									

Notes for Table 1.

bodywt - bodyweight
conc - dietary concentration of PCBs (mg/kg wet weight (ww))
RR - relative response = treatment response / control response
Kit bodyweight is for birth to 1 week age.
TRV - toxicity reference value for dietary PCBs (mg/kg wet weight (ww))

$$\text{Log}_{10}\,\text{TRV} = \text{Log}_{10}\,C_j + (((M_1 * P) - M_j) * ((\text{Log}_{10}\,C_{j+1} - \text{Log}_{10}\,C_j) / (M_{j+1} - M_j)))$$

$$\text{TRV} = 10^{\text{Log}10\,\text{TRV}}$$

Study - lead author, date; see notes for Table 2 for citations

A1254 live kit/mated 1 season M_j of 0.92 is the mean of 1.15 (Wren87) and 0.69 (Aulerich77) both at 1 mg/kg dietary concentration.
Return kit survival 2 season M_j of 0.11 at C_j of 0.75 are the means of 0.05 and 0.16 (M_j) at 0.5 and 1.0 (C_j), respectively.

Table 2. Mink PCB Toxicity Studies

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
1	reported as A1254, from cow	5.2 month	0.64 ppm (control 0.3 ppm)	1.23 ppm liver (control 0.39 ppm); 0.97 ppm muscle (control 0.23 ppm)				0.17		0, 1 d
		3.4 month	3.6 ppm	11.99 ppm liver; 3.31 ppm muscle	0	0	0	0		
2	A1242 product	9.7 month	2 ppm (control NA)		1	1.37	1.43	1.43	0.94 birth	1.42 4 wk
	A1254 product	4.2 month	1 ppm (control NA)		0.8	0.90	0.86	0.69		
		9.7 month	2 ppm (control NA)		0.29	0.24	0.14	0.04	0.55 birth	0 4 wk
		4.2 month	5 ppm (control NA)		0.25	0.50	0.20	0.05		
3	NA (PCB type not identified)	2.2 month	3.3 ppm + 3.3 ppm DDT (control 0.05 ppm)	86 ppm fat (control 14 ppm)	0.79	0.57	0.20	0.17	0.72 birth	0.21 5 d

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			11 ppm	280 ppm fat	0	0	0	0		
4	A1242 product	8.1 month	5 ppm (control NA)		0	0	0	0		
			10 ppm		0	0	0	0		
5	reported as A1254, Green Bay alewife	7 month	0.21 ppm (control 0.09 ppm)	8.1 ppm adipose (control 2.9 ppm)	0.92	1.15	1.26	1.11	1.01 birth 1.02 4 wk	0.93 4 wk
	L Michigan Whitefish	7 month	0.48 ppm	13 ppm adipose	0.89	0.91	0.95	0.84	1.02 birth 0.88 4 wk	0.51 4 wk
	Saginaw Bay sucker	7 month	0.63 ppm	10 ppm adipose	1.00	0.80	0.67	0.66	1.05 birth 0.91 4 wk	0.73 4 wk
	L Erie perch	7 month	0.69	13 ppm adipose	0.91	0.93	0.88	0.79	0.98 birth 0.80 4 wk	0.65 4 wk
	Saginaw Bay carp	7 month	1.5 ppm	37 ppm adipose	0.30	0.56	0	0		
	Erie perch & Saginaw wht sucker	7 month + 1st yr exposure)	0.66 ppm (control 0.04 ppm)		0.58	0.37	0.19	0.11	0.86 birth	0 4 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
6	A1254 product	6.1 month	1 ppm (control 0.02 ppm)	2.8 ppm liver (control 0.09 ppm)	0.99	1.09	1.16	1.15	0.77 1 wk 0.75 3 wk, 0.71 5 wk	1.00 5 wk nearly all starvation (control 75 % trauma or infection, but no starvation)
7	Clophen A50	3 month	12 ppm	181 ppm fat 4.0 ppm muscle	0.11	0.12	0	0		
	A1254	3 month	10 ppm	74 ppm fat 1.3 ppm muscle	0.34	0.66	0	0		
8	PCB - sum of 1242, 1248, 1254, and 1260; TEQ - H4IIE bioassay; Saginaw carp	6 month	PCB 0.72 ppm (control 0.015 ppm); TEQ 19.4 ppt (control 1 ppt)	PCB 2.2 ppm liver (control 0.1 ppm) TEQ 495 ppt (control <10 ppt)	1.00	0.93	0.76	0.76	0.93 birth; 0.67 3 wk; 0.79 6 wk	0.33 6 wk
			PCB 1.53 ppm TEQ 40 ppt	PCB 3.1 ppm liver TEQ 439 ppt	1.00	1.02	0.96	0.96	0.82 birth; 0.67 3 wk 0.41 6 wk	0.13 6 wk
			PCB 2.56 ppm TEQ 80.8 ppt	PCB 6.3 ppm liver TEQ 656 ppt	1.00	0.58	0.14	0.14	0.71 birth	0 3 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
9	PCB - sum of 1242, 1248, 1254, and 1260; TEQ - H4IIE bioassay; Saginaw carp	6 month (P_1 1992)	PCB 0.25 ppm (control 0.02 ppm) TEQ 7.1 ppt (control 1 ppt)		1.36	1.16	1.19	1.66	0.93-0.94 birth 0.75-0.89 3 wk 0.75-0.85 6 wk	 1.06 3 wk 0.93 6 wk
			PCB 0.5 ppm TEQ 13.6 ppt		1.35	1.02	0.91	1.25	0.84-0.87 birth 0.67-0.75 3 wk 0.65-0.68 6 wk	 0.81 3 wk 0.72 6 wk
			PCB 1.0 ppm TEQ 26.4 ppt		1.16	1.02	0.77	0.91	0.75-0.79 birth 0.51-0.59 3 wk 0.35-0.49 6 wk	 0.32 3 wk 0.32 6 wk
		16 month (P_1 1993)	PCB 0.25 ppm TEQ 7.1 ppt	PCB 0.98 ppm liver (control 0.07 ppm)	1.02	0.95	0.96	0.98	0.88-1.09 birth 0.87-0.91 3 wk 0.92 6 wk	 0.99 3 wk 0.95 6 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			PCB 0.5 ppm TEQ 13.6 ppt	PCB 0.89 ppm liver	0.78	0.92	0.80	0.63	0.77-0.81 birth 0.65-0.67 3 wk 0.93 6wk	0.62 3 wk 0.05 6 wk
			PCB 1.0 ppm TEQ 26.4 ppt	PCB 1.57 ppm liver	0.66	0.63	0.59	0.40	0.73-0.74 birth 0.50-0.59 3 wk 0.60-0.66 6 wk	0.15 3 wk 0.16 6 wk
		12 month F_1 of 6-month exposed parents (F_1-1 1993)	PCB 0.25 ppm TEQ 7.1 ppt	PCB 0.63 ppm liver (control 0.02 ppm)	0.85	1.05	0.96	0.84	0.87 birth 1.03-1.10 3 wk 0.89-0.95 6 wk	0.76 3 wk 0.80 6 wk
			PCB 0.5 ppm TEQ 13.6 ppt	PCB 0.96 ppm liver	0.76	0.88	0.31	0.23	0.64-0.73 birth 0.42 3 wk 0.54 6 wk	0.16 3 wk 0.18 6 wk
			PCB 1.0 ppm TEQ 26.4 ppt	1.47	0.63	0.53	0.09	0.07	0.51-0.60 birth	0 3 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
10	reported as A1260 Poplar Creek & Clinch River fish	7 month	0.52 ppm (control <0.005 ppm)	<0.005 ppm liver (control <0.005); NA fat (control 3.2 ppm fat)	0.58	1.20	1.15	0.67	1.02 6 wk	0.79 6 wk
			1.01 ppm	<0.005 ppm liver; 105.86 ppm fat	0.87	0.92	1.10	0.96	0.94 6 wk	1.24
			1.36 ppm	7.25 ppm liver; 128.63 ppm fat	1.16	0.66	0.75	0.87	0.90 6 wk	1.57
11	Clophen A50 product; TEQ calculated by WHO TEFs	6 month	PCB 0.77 ppm (control 0.01 ppm) TEQ 22 ppt		0.96	1.20	1.30	1.24	0.99 birth	
			PCB 2.31 ppm TEQ 65 ppt		0.97	1.04	0.95	0.92	0.82 birth	
		18 month	PCB 0.77 ppm TEQ 22 ppt (NOAEC TEQ 3 ppt)	11 ppm lipid muscle (control <1 ppm)	0.95	1.22	1.34	1.27	0.90 birth 0.69 2 wk 0.67 5 wk	0.49 2 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			PCB 2.31 ppm TEQ 65 ppt	54 ppm	0.42	0.80	0.45	0.20	0.75 birth	0 2 wk
12	reported as PCB (Aroclor not specified); Baltic herring	5.3 month before mating + exposure during mating; TEQ not specified ("internat-ional" TEFs)	PCB 0.36 ppm (control 0.024 ppm) TEQ 26 ppt (control 2 ppt)		1.00	0.92	0.92	0.92	0.87–0.90 10 d 0.87–0.89 50 d	
	A1242 product added to freshwater smelt	5.3 month before mating, control exposure during mating	PCB 2.88 ppm TEQ 157 ppt		0.80	0.76	0.73	0.58	0.78-0.81 10 d 0.95–1.01 50 d	

Notes for Table 2.

Ref - references [abbreviated reference used in the figures and Table 1 in brackets]:

1) [Platonow73] Platonow, N. and L. Karstad. 1973. Dietary effects of polychlorinated biphenyls on mink. Can J Comp Med 37: 391-400.

2) [Aulerich77] Aulerich, R. and R. Ringer. 1977. Current status of PCB toxicity to mink, and effect on their reproduction. Arch Environ Contam Toxicol 6: 279-292.

3) [Jensen77] Jensen, S. 1977. Effect of PCB and DDT on mink (*Mustela vision*) during the reproductive season. Ambio 6: 239.

4) [Bleavins80] Bleavins, M., R. Aulerich, and R. Ringer. 1980. Polychlorinated biphenyls (Aroclors 1016 and 1242): Effects on survival and reproduction in mink and ferrets. Arch Environ Contam Toxicol 9: 627-635.

5) [Hornshw83] Hornshaw, T., R. Aulerich and H. Johnson. 1983. Feeding Great Lakes fish to mink: Effects on mink accumulation and elimination of PCBs by mink. J Toxicol Environ Health 11: 933-946.

6) [Wren87] Wren, C., D. Hunter, J. Leatherland, and P. Stokes. 1987. The effects of polychlorinated biphenyls and methylmercury, singly and in combination on mink. I. uptake and toxic responses. Arch Environ Contam Toxicol 16: 441-447; and II. reproduction and kit development. Arch Environ Contam Toxicol 16: 449-454.

7) [Kihistrm92] Kihiström, J., M. Olsson, S. Jensen, Å. Johansson, J. Ahlbom, and A. Bergman. 1992. Effect of PCB and different fractions of PCB on the reproduction of the mink (*Mustela vison*). Ambio 21: 563-601.

8) [Heaton95] Heaton, S., S. Bursian, J. Giesy, D. Tillitt, J. Render, P. Jones, D. Verbrugge, T. Kubiak and R. Aulerich. 1995. Dietary exposure of mink to carp from Saginaw Bay, Michigan. 1. Effects on reproduction and survival, and the potential risks to wild mink populations. Arch Eviron Contam Toxicol 28: 334-343; and 2.Hematology and liver pathology. Arch Eviron Contam Toxicol 29: 411-417; Tillit, D., R. Gale, J. Meadows, J. Zajicek, P. Peterman, S. Heaton, P. Jones, S. Bursian, T. Kubiak, J. Giesy, and R. Aulerich. 1996. Dietary exposure of mink to carp from Saginaw Bay. 3. Characterization of dietary exposure to planar halogenated hydrocarbons, dioxin equivalents, and biomagnification. Environ Sci Technol 30: 283-291.

9) [Restum98] Restum, J., S. Bursian, J. Giesy, J. Render, W. Helferich, E. Shipp, D. Verbrugge, and R. Aulerich. 1998. Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron, on mink: 1. Effects on mink reproduction, kit growth, and survival, and selected biological parameters. J Toxicol Environ Health Part A 54: 343-375; Shipp, E., J. Restum, J. Giesy, S. Bursian, R. Aulerich, and W. Helferich. 1998. Multigenerational study of the effects of consumption of PCB-contaminated carp from Saginaw Bay, Lake Huron, on mink. 2. Liver PCB concentration and induction of hepatic cytochrome P-450 activity as a potential biomarker for PCB exposure. J Toxicol Environ Health Part A 54: 377-401; Tillit, D., R. Gale, J. Meadows, J. Zajicek, P. Peterman, S. Heaton, P. Jones, S. Bursian, T. Kubiak, J. Giesy, and R. Aulerich. 1996. Dietary exposure of mink to carp from Saginaw Bay. 3. Characterization of dietary exposure to planar halogenated hydrocarbons, dioxin equivalents, and biomagnification. Environ Sci Technol 30: 283-291.

TEQ for Restum, et al. (1998) based on the following regression of total PCB (ppm) and H4IIE-bioassay TEQ (ppt) (data from Tillit, et al. 1996):
TEQ = (25.735 * PCB) + 0.703 $r^2 = 1.0$, $p = 0.005$, for PCB range 0.015–1.53 ppm

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11) [Brunstm01] Brunström, B., B. Lund, A. Bergman, L. Asplund, I. Athanassiadis, M. Athanasiadou, S. Jensen, and J. Örberg. 2001. Reproductive toxicity in mink (*Mustela vison*) chronically exposed to environmentally relevant polychlorinated biphenyl concentrations. Environ Toxicol Chem 20: 2318-2327. An earlier report is Brunström, B., A. Bergman, Bäcklin, B., B. Lund, and J. Örberg. 1994. Effects of long-term exposure to PCB and PCB methylsulfones on reproduction in the mink. *In*: Dioxin '94, 14th International Symposium on Chlorinated Dioxins, PCB and Related Compounds (H. Fiedler, ed.). Short Papers. Organohalogen Compounds 20: 471-473. [Data are exclusively taken from 2001].

12) [Kakela02] Käkelä, A., R. Käkelä, H. Hyvärinen, and J. Asikainen. 2002. Vitamins A_1 and A_2 in hepatic tissue and subcellular fractions in mink feeding on fish-based diets and exposed to Aroclor 1242. Environ Toxicol Chem 21: 397-403.

Relative Response Compared to Control = treatment response / control response

Source: product is commercial product mixed with food; field is field-contaminated biota prepared as food

Lead author Date	Chemical	Dietary PCB conc. mg/kg ww	Treatment name	Chemical source	Dietary TEQ conc. pg/g ww	TEQ source	Exposure duration month	Breeding seasons exposed	Generations exposed	Tissue	Tissue residue PCB conc. mg/kg ww	Lipid cont. % ww	PCB conc. mg/kg lw	TEQ conc. ww	Whelp frequency Control %	Treatment %	RR ratio	Whelp freq. source	Total kl Control number
Platonow73	A1254	0.64		field			5.2	1	1	liver, muscle	1.23, 0.97								
Platonow73	A1254	3.57		field			3.4	1	1	liver, muscle	11.99, 3.31				NA	0	0.00	text p 393	NA
Aulerich77	A1242	2		product			9.7	1	1						100	100	1.00	table 10	4.1
Aulerich77	A1254	1		product			4.2	1	1						100	80	0.80	table 9	6
Aulerich77	A1254	2		product			9.7	1	1						100	29	0.29	table 10	4.1
Aulerich77	A1254	5		product			4.2	1	1						100	25	0.25	table 9	6
Jensen77	NA	3.3	Group B	NA			2.2	1	1	adipose			86		92	73	0.79	table 1	5.1
Jensen77	NA	11	Goup C	NA			2.2	1	1	adipose			280		92	0	0.00	table 1	5.1
Bleavins80	A1242	5		product			8.1	1	1						76.2	0	0.00	table 2	5.8
Bleavins80	A1242	10		product			8.1	1	1						76.2	0	0.00	table 2	5.8
Hornshw83	A1254	0.21	alewife	field			7	1	1	adipose			8.1		90	83	0.92	table 3	5.4
Hornshw83	A1254	0.48	whitefish	field			7	1	1	adipose			13		90	80	0.89	table 3	5.4
Hornshw83	A1254	0.63	sucker	field			7	1	1	adipose			10		90	90	1.00	table 3	5.4
Hornshw83	A1254	0.69	perch	field			7	1	1	adipose			13		90	82	0.91	table 3	5.4
Hornshw83	A1254	1.5	carp	field			7	1	1	adipose			37		90	27	0.30	table 3	5.4
Hornshw83	A1254	0.66	perch/sucker	field			7	2	1						88	50	0.58	table 3	5.4
Wren87	A1254	1	PCB	product			6.1	1	1	liver	2.8				93	92	0.99	87b table 2	6.9
Kihlstrm92	A50	12	Group 2	product			3	1	1	muscle	3.98	2.2	181.00		90	10	0.11	table 2	8.1
Kihlstrm92	A1254	10	Group 9	product			3	1	1	muscle	1.33	1.8	74.00		89	30	0.34	table 2	5
Heaton95	PCB	0.72	10 % carp	field	19.4	H4IIE	6	1	1	liver	2.2			495	50	50	1.00	p 335, table 2	5.7
Heaton95	PCB	1.53	20 % carp	field	40	H4IIE	6	1	1	liver	3.1			439	50	50	1.00	p 335, table 2	5.7
Heaton95	PCB	2.56	30 % carp	field	80.8	H4IIE	6	1	1	liver	6.3			656	50	50	1.00	p 335, table 2	5.7
Restum98	PCB	0.25	P1 0.25 to F1-1	field	7.1	H4IIE	6	1	1						69	94	1.36	table 6	5
Restum98	PCB	0.5	P1 0.5 to F1-1	field	13.6	H4IIE	6	1	1						69	93	1.35	table 6	5
Restum98	PCB	1	P1 1.0 to F1-1	field	26.4	H4IIE	6	1	1						69	80	1.16	table 6	5
Restum98	PCB	0.25	P1 0.25-0.25 to F1-2	field	7.1	H4IIE	16	2	1	liver	0.98				86	88	1.02	table 6	6.3
Restum98	PCB	0.5	P1 0.5-0.5 to F1-2	field	13.6	H4IIE	16	2	1	liver	0.89				86	67	0.78	table 6	6.3
Restum98	PCB	1	P1 1.0-1.0 to F1-2	field	26.4	H4IIE	16	2	1	liver	1.57				86	57	0.66	table 6	6.3
Restum98	PCB	0.25	F1-1 0.25-0.25 to F2	field	7.1	H4IIE	12	2	2	liver	0.63				79	67	0.85	table 6	5.7
Restum98	PCB	0.5	F1-1 0.5-0.5 to F2	field	13.6	H4IIE	12	2	2	liver	0.96				79	60	0.76	table 6	5.7
Restum98	PCB	1	F1-1 1.0-1.0 to F2	field	26.4	H4IIE	12	2	2	liver	1.47				79	50	0.63	table 6	5.7
Halbrok99	A1260	0.52	Diet C	field			7	1	1	liver	<0.005				86	50	0.58	text p 652, table 2	6.5
Halbrok99	A1260	1.01	Diet D	field			7	1	1	liver, fat	<0.005		105.86		86	75	0.87	text p 652, table 2	6.5
Halbrok99	A1260	1.36	Diet E	field			7	1	1	liver, fat	7.25		128.63		86	100	1.16	text p 652, table 2	6.5
Brunstm01	A50	0.77	A50 low	product	22	WHO	6	1	1						93	89	0.96	table 3	4.9
Brunstm01	A50	2.31	A50 high	product	65	WHO	6	1	1						93	90	0.97	table 3	4.9
Brunstm01	A50	0.77	A50 low	product	22	WHO	18	2	1	muscle	0.26	2.4	11		93	88	0.95	table 5	5.1
Brunstm01	A50	2.31	A50 high	product	65	WHO	18	2	1	muscle	1.30	2.4	54		93	39	0.42	table 5	5.1
Kakela02	PCB	0.36	Baltic herring	field	26	NA	5.3	1	1						100	100	1.00	table 3	6.6
Kakela02	A1242	2.88	Smelt PCB	product	157	NA	5.3	1	1						100	80	0.80	table 3	6.6

Notes:
Treatment data only, control data excluded (control RR = 1.0 by definition)
TEQ source - H4IIE - rat hepatoma cell bioassay; WHO - Van den Berg, et al. (1998)
Exposure duration - month = days / 30.5 or weeks / 4; PCB - sum of multiple Aroclors; NA - not available
RR - relative response = treatment response / control response
Default Live kits/mated female = Live kits/whelped female * fraction of females whelped
Plantonow73 - Treatment 0.64 Live kits/mated female = 3 kits / 10 females surviving (2 deaths out of 12 during breeding)
Jensen77 - PCB type or source not identified; Live kits/whelped female = No. of whelps born/pregnant female - number of stillbirths/bitch
Hornshaw83 - Tissue residue for February 1980, mean values
Kihlstrm92 - Dietary PCB conc. = 2 mg A50/d or 1.64 mg A1254/d / 0.17 kg food/d (p. 564); Table 2 Stillborn should be 1 (not 100) for Group 2 (fig 4)
Heaton95 - Liver conc. from Tillitt, et al. 96 (Table 4)
Restum98 - Treatment name is parental designation to offspring designation; TEQ interpolated from Tillitt, et al. 96 (Tables 1 and 2)
Restum98 - Live kits/whelped female = Survivability at birth * Litter size
Restum98 - Kit bodyweight in order of male, female kit; -- no survivors; RR is the unweighted mean of male and female RRs, or single sex RR if only one sex survived
Halbrook99 - Diet A is used for control; Kit survival = (Alive at 6 weeks / Born alive) * 100
Brunstm01 - Dietary PCB conc. = 0.1 or 0.3 mg A50/d / 0.13 kg/d food ration (p. 2319)
Kakela02 - Smelt PCB treatment was exposed for 21 wk before breeding, then switched to control diet during breeding
Kakela02 - Dietary PCB conc. = Sum PCB per day / Average food consumption; Kit bodyweight in order of male kit, female kit; RR is unweighted mean
Kakela02 - Live kits/whelped female = ((Kits/mother * surviving females) - Dead kits) / surviving females; TEQ - "international" TEFs but no date is given

Lead author Date	Chemical	Dietary PCB conc. mg/kg ww	Treatment name	ts / whelped female Treatment number	RR ratio	Total kits / whelped source	Live kits / whelped female Control number	Treatment number	RR ratio	Live kits / whelped source	Live kits / mated female Control number	Treatment number	RR ratio	Live kits / mated source	Kit bodyweight 0-1 wk Control g	Treatment g	RR ratio	Kit bodyweight 2-3 wk Control g	Treatment g	RR ratio	Kit b Control g
Platonow73	A1254	0.64									1.8	0.3	0.17	text p 393, 398							
Platonow73	A1254	3 57		0	0.00	text p 393	NA	0	0.00	text p 393	1.8	0	0.00	text p 393, 398							
Aulerich77	A1242	2		5.6	1.37	table 10	3.5	5	1.43	table 10	3.5	5	1.43	table 10	9.9	9.3	0.94				
Aulerich77	A1254	1		5.4	0.90	table 9	5.1	4.4	0.86	table 9	5.1	3.5	0.69	table 9							
Aulerich77	A1254	2		1	0.24	table 10	3.5	0.5	0.14	table 10	3.5	0.14	0.04	table 10	9.9	5.4	0.55				
Aulerich77	A1254	5		3	0.50	table 9	5.1	1	0.20	table 9	5.1	0.25	0.05	table 9							
Jensen77	NA	3.3	Group B	2.9	0.57	table 1	4.6	0.9	0.20	text, table 1	4.2	0.7	0.17	text, table 1	9.4	6.8	0.72				
Jensen77	NA	11	Goup C	0	0.00	table 1	4.6	0	0.00	text, table 1	4.2	0	0.00	text, table 1							
Bleavins80	A1242	5		0	0.00	table 2	4 9	0	0.00	table 2	3.8	0	0.00	table 2							
Bleavins80	A1242	10		0	0.00	table 2	4.9	0	0.00	table 2	3.8	0	0.00	table 2							
Hornshw83	A1254	0.21	alewife	6.2	1.15	table 3	4.2	5.3	1.26	table 3	3.8	4.2	1.11	table 3	8.3	8.4	1.01				122
Hornshw83	A1254	0.48	whitefish	4 9	0.91	table 3	4 2	4	0.95	table 3	3.8	3.2	0.84	table 3	8.3	8.5	1.02				122
Hornshw83	A1254	0 63	sucker	4 3	0.80	table 3	4.2	2.8	0.67	table 3	3.8	2.5	0.66	table 3	8.3	8.7	1.05				122
Hornshw83	A1254	0.69	perch	5	0.93	table 3	4.2	3.7	0.88	table 3	3.8	3	0.79	table 3	8.3	8.1	0.98				122
Hornshw83	A1254	1.5	carp	3	0.56	table 3	4.2	0	0.00	table 3	3.8	0	0.00	table 3							
Hornshw83	A1254	0.66	perch/sucker	2	0.37	table 3	5.2	1	0.19	table 3	4.4	0.5	0.11	table 3	9	7.7	0.86				
Wren87	A1254	1	PCB	7 5	1.09	87b table 2	5.8	6.7	1.16	87b table 2	5.4	6.2	1.15	87b table 2	28.1	21.6	0.77	107.3	80.2	0.75	227.8
Kihistrm92	A50	12	Group 2	1	0.12	table 2	5 3	0	0.00	table 2	4.8	0	0.00	table 2							
Kihistrm92	A1254	10	Group 9	3 3	0.66	table 2	4 3	0	0.00	table 2	3.7	0	0.00	table 2							
Heaton95	PCB	0.72	10 % carp	5 3	0.93	table 2	5	3.8	0.76	table 2	2.5	1.9	0.76	p 335, table 2	10.5	9.76	0.93	98.7	66.1	0.67	248
Heaton95	PCB	1.53	20 % carp	5.8	1.02	table 2	5	4.8	0.96	table 2	2.5	2.4	0.96	p 335, table 2	10.5	8.66	0.82	98.7	65.8	0.67	248
Heaton95	PCB	2.56	30 % carp	3.3	0 58	table 2	5	0.7	0 14	table 2	2.5	0.35	0.14	p 335, table 2	10.5	7.49	0.71				
Restum98	PCB	0.25	P1 0.25 to F1-1	5.8	1 16	table 6	4 7	5.6	1.19	tables 6, 7	3.2	5.3	1.66	table 6	10, 9.2	9.3, 8.7	0.94	113, 99	89, 88	0.84	293, 253
Restum98	PCB	0.5	P1 0.5 to F1-1	5.1	1.02	table 6	4 7	4.3	0.91	tables 6, 7	3.2	4	1.25	table 6	10, 9.2	8.7, 7.7	0.86	113, 99	76, 74	0.71	293, 253
Restum98	PCB	1	P1 1.0 to F1-1	5 1	1.02	table 6	4 7	3.6	0.77	tables 6, 7	3.2	2.9	0.91	table 6	10, 9.2	7.5, 7.3	0.77	113, 99	58, 58	0.55	293, 253
Restum98	PCB	0.25	P1 0.25-0.25 to F1-2	6	0.95	table 6	5.6	5.4	0.96	tables 6, 7	4.8	4.7	0.98	table 6	11.1, 9.9	9.8, 10.8	0.99	116, 110	106, 96	0.89	340, 304
Restum98	PCB	0.5	P1 0.5-0.5 to F1-2	5.8	0.92	table 6	5.6	4.5	0.80	tables 6, 7	4.8	3	0.63	table 6	11.1, 9.9	8.6, 8.0	0.79	116, 110	78, 72	0.66	340, 304
Restum98	PCB	1	P1 1.0-1.0 to F1-2	4	0.63	table 6	5.6	3.3	0.59	tables 6, 7	4.8	1.9	0.40	table 6	11.1, 9.9	8.1, 7.3	0.74	116, 110	69, 55	0.55	340, 304
Restum98	PCB	0.25	F1-1 0.25-0.25 to F2	6	1.05	table 6	5.5	5.3	0.96	tables 6, 7	4.3	3.6	0.84	table 6	9.8, 9.2	8.5, 8.0	0.87	116, 106	128, 109	1.07	380, 326
Restum98	PCB	0.5	F1-1 0.5-0.5 to F2	5	0.88	table 6	5.5	1.7	0.31	tables 6, 7	4.3	1	0.23	table 6	9.8, 9.2	7.2, 5.9	0.69	116, 106	–, 45	0.42	380, 326
Restum98	PCB	1	F1-1 1.0-1.0 to F2	3	0.53	table 6	5.5	0.5	0.09	tables 6, 7	4.3	0.3	0.07	table 6	9.8, 9.2	5.0, 5.5	0.56				
Halbrok99	A1260	0.52	Diet C	7.8	1 20	table 2	5 2	6	1.15	table 2	4.5	3	0.67	text p 652, table 2							328
Halbrok99	A1260	1.01	Diet D	6	0.92	table 2	5.2	5.7	1.10	table 2	4.5	4.3	0.96	text p 652, table 2							328
Halbrok99	A1260	1.36	Diet E	4 3	0.66	table 2	5 2	3.9	0.75	table 2	4.5	3.9	0.87	text p 652, table 2							328
Brunstm01	A50	0.77	A50 low	5.9	1.20	table 3	4	5.2	1.30	table 3	3.7	4.6	1.24	table 3	9.6	9.5	0.99				
Brunstm01	A50	2.31	A50 high	5.1	1.04	table 3	4	3.8	0.95	table 3	3.7	3.4	0.92	table 3	9.6	7.9	0.82				
Brunstm01	A50	0.77	A50 low	6.2	1.22	table 5	4.4	5.9	1.34	table 5	4.1	5.2	1.27	table 5	8.9	8	0.90	70	48	0.69	258
Brunstm01	A50	2.31	A50 high	4.1	0.80	table 5	4.4	2	0.45	table 5	4.1	0.8	0.20	table 5	8.9	6.7	0.75				
Kakela02	PCB	0.36	Baltic herring	6.1	0.92	table 3	6.6	6.1	0.92	table 3	6.6	6.1	0.92	table 3				63, 58	55, 52	0.89	566, 505
Kakela02	A1242	2.88	Smelt PCB	5	0.76	table 3	6.6	4.8	0.73	table 3	6.6	3.8	0.58	table 3				63, 58	49, 47	0.80	566, 505

Lead author Date	Chemical	Dietary PCB conc. mg/kg ww	Treatment name	dyweight 4-6 wk Treatment g	RR ratio	Kit bodyweight source	Control %	Kit survival Treatment %	RR ratio	Kit survival source
Platonow73	A1254	0.64					NA	0	0.00	text p 393
Platonow73	A1254	3.57								
Aulerich77	A1242	2				table 10	64	91	1.42	table 10
Aulerich77	A1254	1								
Aulerich77	A1254	2				table 10	64	0	0.00	table 10
Aulerich77	A1254	5								
Jensen77	NA	3.3	Group B			text	82	17	0.21	text
Jensen77	NA	11	Goup C							
Bleavins80	A1242	5								
Bleavins80	A1242	10								
Hornshw83	A1254	0.21	alewife	124	1.02	table 4	55	51	0.93	table 3
Hornshw83	A1254	0.48	whitefish	107	0.88	table 4	55	28	0.51	table 3
Hornshw83	A1254	0.63	sucker	111	0.91	table 4	55	40	0.73	table 3
Hornshw83	A1254	0.69	perch	98	0.80	table 4	55	36	0.65	table 3
Hornshw83	A1254	1.5	carp							
Hornshw83	A1254	0.66	perch/sucker			table 4	65	0	0.00	table 3
Wren87	A1254	1	PCB	161.2	0.71	87b table 4	72	72.2	1.00	87b table 2
Kihistrm92	A50	12	Group 2							
Kihistrm92	A1254	10	Group 9							
Heaton95	PCB	0.72	10 % carp	197	0.79	table 3	85	28	0.33	table3
Heaton95	PCB	1.53	20 % carp	101	0.41	table 3	85	11	0.13	table3
Heaton95	PCB	2.56	30 % carp			table 3	85	0	0.00	table3
Restum98	PCB	0.25	P1 0.25 to F1-1	220, 214	0.80	table 8	72.7	67.8	0.93	table 7 wk 6
Restum98	PCB	0.5	P1 0.5 to F1-1	200, 165	0.67	table 8	72.7	52.5	0.72	table 7 wk 6
Restum98	PCB	1	P1 1.0 to F1-1	102, 125	0.42	table 8	72.7	23	0.32	table 7 wk 6
Restum98	PCB	0.25	P1 0.25-0.25 to F1-2	312, 280	0.92	table 9	80.3	76.2	0.95	table 7 wk 6
Restum98	PCB	0.5	P1 0.5-0.5 to F1-2	317, –	0.93	table 9	80.3	4.4	0.05	table 7 wk 6
Restum98	PCB	1	P1 1.0-1.0 to F1-2	223, 182	0.63	table 9	80.3	12.5	0.16	table 7 wk 6
Restum98	PCB	0.25	F1-1 0.25-0.25 to F2	361, 291	0.92	table 10	73	58.3	0.80	table 7 wk 6
Restum98	PCB	0.5	F1-1 0.5-0.5 to F2	–, 177	0.54	table 10	73	13.3	0.18	table 7 wk 6
Restum98	PCB	1	F1-1 1.0-1.0 to F2			table 10	73	0	0.00	table 7 wk 6
Halbrok99	A1260	0.52	Diet C	333	1.02	table 2	63.5	50	0.79	table 2
Halbrok99	A1260	1.01	Diet D	307	0.94	table 2	63.5	78.9	1.24	table 2
Halbrok99	A1260	1.36	Diet E	295	0.90	table 2	63.5	100	1.57	table 2
Brunstm01	A50	0.77	A50 low			table 3				
Brunstm01	A50	2.31	A50 high			table 3				
Brunstm01	A50	0.77	A50 low	173	0.67	table 5, fig 2	73	36	0.49	text p 2322
Brunstm01	A50	2.31	A50 high			table 5	73	0	0.00	text p 2322
Kakela02	PCB	0.36	Baltic herring	501, 439	0.88	table 3				
Kakela02	A1242	2.88	Smelt PCB	573, 481	0.98	table 3				

AUTHOR$	CHEMICAL$	SOURCE$	MONTHS	CONTINUO	SEASON$	GENERATIO	DURATION$	DIETPCB	DIETTEQ	TISPCBWW	TISSUE$	TISPCBL	TISTEQWW	TEQTYPE$	WHELPFRET	KITWHELP	LKITWHELP	LKITMATE	KITBW1WK	KITBW2WK	KITBW4WK	KITSURV
Platonow73	A1254	field	5 2	Y	1	1		0 3		0 39	liver				1	1	1	1				1
Platonow73	A1254	field	5 2	Y	1	1		0 64		1 23	liver							0 17				0 01
Platonow73	A1254	field	3 4	Y	1	1		3 57		11 99	liver				0 01	0 01	0 01	0 01				
Aulench77	A1242	product	9 7	Y	1	1		2							1	1 37	1 43	1 43	0 94			1 42
Aulench77	A1254	product	4 2	Y	1	1		1							0 8	0 9	0 86	0 69				
Aulench77	A1254	product	9 7	Y	1	1		2							0 29	0 24	0 14	0 04	0 55			0 01
Aulench77	A1254	product	4 2	Y	1	1		5							0 25	0 5	0 2	0 05				
Jensen77	NA	NA	2 2	Y	1	1		0 05			adipose	14			1	1	1	1	1			1
Jensen77	NA	NA	2 2	Y	1	1		3 3			adipose	86			0 79	0 57	0 2	0 17	0 72			0 21
Jensen77	NA	NA	2 2	Y	1	1		11			adipose	280			0 01	0 01	0 01	0 01				
Bleavins80	A1242	product	8 1	Y	1	1		5							0 01	0 01	0 01	0 01				
Bleavins80	A1242	product	8 1	Y	1	1		10							0 01	0 01	0 01	0 01				
Hornshw83	A1254	field	7	Y	1	1		0 09			adipose	2 9			1	1	1	1	1		1	1
Hornshw83	A1254	field	7	Y	1	1		0 21			adipose	8 1			0 92	1 15	1 26	1 11	1 01		1 02	0 93
Hornshw83	A1254	field	7	Y	1	1		0 48			adipose	13			0 89	0 91	0 95	0 84	1 02		0 88	0 51
Hornshw83	A1254	field	7	Y	1	1		0 63			adipose	10			1	0 8	0 67	0 68	1 05		0 91	0 73
Hornshw83	A1254	field	7	Y	1	1		0 69			adipose	13			0 91	0 93	0 88	0 79	0 98		0 8	0 65
Hornshw83	A1254	field	7	Y	1	1		1 5			adipose	37			0 3	0 56	0 01	0 01				
Hornshw83	A1254	field	7	Y	2	1		0 04							1	1	1	1	1			1
Hornshw83	A1254	field	7	Y	2	1		0 66							0 58	0.37	0 19	0 11	0 86			0 01
Wren87	A1254	product	6 1	Y	1	1		0 02		0 09	liver				1	1	1	1	1	1	1	1
Wren87	A1254	product	6 1	Y	1	1		1		2 8	liver				0 99	1.09	1 16	1 15	0 77	0 75	0 71	1
Kihistrm92	A50	product	3	Y	1	1		12		3 98	muscle	181			0 11	0.12	0 01	0 01				
Kihistrm92	A1254	product	3	Y	1	1		10		1 33	muscle	74			0 34	0 66	0 01	0 01				
Heaton95	PCB	field	6	Y	1	1		0 015	1	0 1	liver		5	H4IIE	1	1	1	1	1	1	1	1
Heaton95	PCB	field	6	Y	1	1		0 72	19 4	2 2	liver		495	H4IIE	1	0 93	0 78	0 76	0 93	0 67	0 79	0 33
Heaton95	PCB	field	6	Y	1	1		1 53	40	3 1	liver		439	H4IIE	1	1 02	0 96	0 96	0 82	0 67	0 41	0 13
Heaton95	PCB	field	6	Y	1	1		2 56	80 8	6 3	liver		656	H4IIE	1	0 58	0 14	0 14	0 71			0 01
Restum98	PCB	field	6	Y	1	1	1 Season	0 02	1						1	1	1	1	1	1	1	1
Restum98	PCB	field	6	Y	1	1	1 Season	0 25	7 1						1 38	1 16	1 19	1 66	0 94	0 84	0 8	0 93
Restum98	PCB	field	6	Y	1	1	1 Season	0 5	13 6						1 35	1 02	0 91	1.25	0 86	0 71	0 67	0 72
Restum98	PCB	field	6	Y	1	1	1 Season	1	26 4						1 16	1 02	0 77	0 91	0 77	0 55	0 42	0 32
Restum98	PCB	field	16	Y	2	1	2 Season	0 02	1	0 07	liver				1	1	1	1	1	1	1	1
Restum98	PCB	field	16	Y	2	1	2 Season	0 25	7 1	0 98	liver				1 02	0 95	0 96	0 98	0 99	0 89	0 92	0 95
Restum98	PCB	field	16	Y	2	1	2 Season	0 5	13 6	0 89	liver				0 78	0 92	0 8	0 83	0 79	0 66	0 93	0 05
Restum98	PCB	field	16	Y	2	1	2 Season	1	26 4	1 57	liver				0 66	0 63	0 59	0 4	0 74	0 55	0 63	0 16
Restum98	PCB	field	12	Y	2	2	2 Generatio	0 02	1	0 02	liver				1	1	1	1	1	1	1	1
Restum98	PCB	field	12	Y	2	2	2 Generatio	0 25	7 1	0 63	liver				0 85	1 05	0 96	0 84	0 87	1 07	0 92	0 8
Restum98	PCB	field	12	Y	2	2	2 Generatio	0 5	13 6	0 96	liver				0 76	0 88	0 31	0 23	0 69	0 42	0 64	0 18
Restum98	PCB	field	12	Y	2	2	2 Generatio	1	26 4	1 47	liver				0 63	0 53	0 09	0 07	0 56			0 01
Halbrok99	A1260	field	7	Y	1	1		0 0025		0 0025	liver				1	1	1	1			1	1
Halbrok99	A1260	field	7	Y	1	1		0 52		0 0025	liver				0 58	1 2	1 15	0 67			1 02	0 79
Halbrok99	A1260	field	7	Y	1	1		1 01		0 0025	liver	105 86			0 87	0 92	1 1	0 96			0 94	1 24
Halbrok99	A1260	field	7	Y	1	1		1 36		7 25	liver	128 63			1 16	0 68	0 75	0 87			0 9	1 57
Brunstm01	A50	product	6	Y	1	1		0 01							1	1	1	1	1			
Brunstm01	A50	product	6	Y	1	1		0 77	22						0 96	1 2	1 3	1 24	0 99			
Brunstm01	A50	product	6	Y	1	1		2 31	65						0 97	1 04	0 95	0 92	0 82			
Brunstm01	A50	product	18	Y	2	1		0 01	3	0 012	muscle	0 5		WHO	1	1	1	1	1	1	1	1
Brunstm01	A50	product	18	Y	2	1		0 77	22	0 26	muscle	11		WHO	0 95	1 22	1 34	1 27	0 9	0 69	0 67	0 49
Brunstm01	A50	product	18	Y	2	1		2 31	65	1 3	muscle	54		WHO	0 42	0 8	0 45	0 2	0 75			0 01
Kakela02	PCB	field	5 3	Y	1	1		0 024	2					NA	1	1	1	1		1	1	
Kakela02	PCB	field	5 3	Y	1	1		0 36	26					NA	1	0 92	0 92	0 92		0 89	0 88	
Kakela02	A1242	product	5 3	N	1	1		2 88	157					NA	0 8	0 76	0 73	0 58		0 8	0 98	

JAMES CHAPMAN To: Tala Henry, Mark Sprenger, Glenn Suter, Dale Hoff, Chris Cubbison cc
10/02/2002 03:38 PM Subject: Peer review charge 2

In this message I attached several files related to the chicken TRV. PCB chicken TRV sum.wpd is the workproduct you are reviewing.

Although the peer review is for the methodology only, not the underlying data, I have attached several spreadsheets in case you want to check anything I did. PCB chick RR.123 documents the data sources and shows the relative response calculations. PCB chicken graph file.123 is a translation of the SYSTAT file I used to generate the dose-response plots. PCB chick linear interpol TRV2.123 shows the TRV calculation for both the log-linear approach I used in the memo, and the linear approach in the guidance.

I will be in the field the rest of this week, and will be on vacation the next week, returning to the office after Columbus Day. If anyone needs a copy of any of the papers I cited, please contact my supervisor Larry Schmitt (he has all the mink and chicken studies I used, the Leonards, et al. paper, and a copy of the linear interpolation section of the effluent testing guidance (I misplaced Klemms, et al., but he has a copy of Chapman, et al.).

Please contact Shari Kolak during my absence if there are scheduling issues.

I sent an earlier message with the mink files and the peer review charge.

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PCB chicke graph file.12 PCB chick RR.123 (Table 2) PCB chick linear interpol TRV2.1 (Table 1) PCB chicken TRV sum.wpd

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 5

DATE: September 23, 2002

SUBJECT: Revised Avian PCB Toxicity Reference Value (TRV)

FROM: James Chapman, Ph.D., Ecologist

TO: Shari Kolak, RPM

Recommended Avian PCB Toxicity Reference Values

The recommended PCB TRVs for birds are 0.1 mg/kg$_{BW}$-d for no effects, and 0.5 mg/kg$_{BW}$-d for low effects, based on A1248.

TRVs calculated from exposure to commercial PCB products may underestimate the toxicity of PCBs in the field because of weathering and selective retention in biota. Effects may also be underestimated due to the relatively short-term exposure durations of the majority of chicken studies (6 to 9 weeks). A single study continued exposure for 39 weeks in a single treatment, which showed increased adverse effects in the final weeks (Fig. 2 in Platonow and Reinhart 1973). However, since chicken are the most sensitive avian species tested to date to PCBs, application of uncertainty factors is not recommended for interspecific or subchronic-to-chronic extrapolations.

Summary

An issue raised concerning the Baseline Ecological Risk Assessment for the Allied Paper, Inc./Portage Creek/Kalamazoo River Superfund site is the appropriate toxicity reference value (TRV) for PCBs in birds. This memo presents an analysis of the effects of PCBs on chicken, one of the best-studied and most sensitive avian receptor of the few species investigated to date.

TRVs are derived from dose-response curves by interpolation of the effective dose to hens (ED_x) or effective concentration in eggs (EC_x) that corresponds to specific relative responses (calculated as the treatment response divided by the control response). The low-effect level is defined as 0.75 of the control response for any toxicological endpoint (ED_{75} or EC_{75}), and the no-effect level as equal to the control response (ED_{100} or EC_{100}) (or the treatment response closest to the ED_{100} or EC_{100}).

A1248 TRVs range from 0.1 to 0.5 mg/kg$_{BW}$-d (no effect to low effect) for egg hatchability. The A1248 TRVs for chick bodyweight are similar: 0.1 to 0.6 mg/kg$_{BW}$-d, but the TRVs for chick survival are lower: 0.1 to 0.3 mg/kg$_{BW}$-d. However, the bodyweight and survival TRVs are based on sparse data (2 mean treatment responses each) compared to hatchability (9 mean treatment responses). The egg TRVs are 0.5 to 1.3 mg A1248/kg whole egg, ww, for hatchability (5 mean treatment responses) (Table 1).

A1254 has higher hatchability TRVs compared to the other Aroclors considered: 0.3 to 1.2 mg/kg_{BW}-d and 8 to 12 mg/kg egg (each based on 5 mean treatment responses) (Table 1). Chick bodyweight or survival data are not available for A1254.

A1242 exhibits two patterns: one similar to A1248 with hatchability TRVs of 0.1 to 0.4 mg/kg_{BW}-d (9 mean treatment responses from two sets of investigators) and 0.7 to 1.5 mg/kg egg (6 mean treatment responses), and another approaching that of A1254 with hatchability TRVs of 0.4 to 0.8 mg/kg_{BW}-d (5 mean treatment responses from a single investigator). The two A1242 patterns may be due to differences in the A1242 batches used by different investigators, chickens, feed, or experimental designs. The A1242 TRVs for chick bodyweight should be interpreted with caution–the dose TRVs, 0.1 to 0.9 mg/kg_{BW}-d, are based on a sparse data (2 mean treatment responses), and the egg TRVs, 0.7 to 10 mg/kg (4 mean treatment responses), are based on a combination of effects on 17-day embryo bodyweight from yolk injection and 3-week chick bodyweight from parental exposure.

Methods

Study results are selected according to the following criteria: 1) studies published in journals (gray literature excluded), 2) matched control and treatment responses, 3) continuous PCB exposure (responses following cessation of exposure are excluded), and 4) treatment responses individually reported (responses based on combinations of dose levels or different Aroclor treatments are excluded). Statistical significance is not a criterion for selection since the objective is to develop dose- or exposure-response relationships over the full gradient tested. When data are reported for more than one exposure time, response data for later exposure periods take precedence over earlier exposure periods or data averaged over the entire exposure period. Data are taken from text, tables, or figures so long as the selection criteria are met.

The dietary PCB concentrations are converted to bodyweight-normalized doses by multiplying by the food ingestion rate reported in the study, or by a default leghorn hen food ingestion rate of 0.067 kg feed/kg_{BW}-d (Medway and Kare 1959). PCB concentration in egg yolk is converted to whole-egg concentration by multiplying by 0.364, the proportion of yolk in chicken eggs (Sotherland and Rahn 1987).

Treatment responses are normalized relative to the respective control responses (relative response = treatment response / control response) so that multiple studies may be compared on a common basis (for example, Leonards, et al. 1995) (Table 2). TRVs are defined in terms of percent response relative to control: 100 % is the no-effect level, and 75 % is the low-effect level (ED_{75})–an alternative to the lowest observed adverse effect level (LOAEL) [1]. The ED_{75} is derived from the dose-response curves by a log-linear interpolation between the responses that bracket the 75 % effect level, a modification of the linear interpolation method used for estimating the chronic

[1] The difference between a LOAEL and the 75 % effect level is that the former is based on a statistically discernible difference between treatment and control response, regardless of the particular effect level, while the latter is based on a specified effect level on a dose- or exposure-response curve. The latter approach is referred to as "ED_x" or "EC_x" (ED–effective dose, EC–effective concentration, x–selected effect level).

toxicity of effluents [2] (Klemm, et al. 1994). Interpolation is performed only when the target value falls within the linear portion of the exposure response plots. No-effect levels are either taken directly from the table if the treatment response does not exceed the control response (but has a relative response >0.9), or is interpolated for the ED_{100} if the treatment response exceeds the control response (relative response > 1.0). Doses or effects are not extrapolated beyond the existing data ranges.

Curve-fitting is not done because each of the data points represents a mean response. The appropriate database for curve-fitting is the underlying replicate data of the various studies, which are not available in the publications.

The results of chicken studies are plotted below. Dose-response relationships are evident for hatchability (Figures 1-8) and chick bodyweight (low chick bodyweight is inversely related to potential survival in the field) (Figures 9-11). An effect on chick survival is apparent for A1248, but not other Aroclors, however all of the chick survival results are based on scant data (only 2 mean treatment responses each) (Figure 12). There are no consistent dose-response relationships for egg productivity or fertility (Figures 13-14), but note that the single treatment showing depressed fertility is from the only long-term PCB chicken study (Platonow and Reinhart 1973) included in the compilation. Although trends are apparent for chick deformity rates, studies were not performed at hen doses sufficiently high to allow interpolation of ED_{75}, except for the field study using Saginaw Bay carp feed (Figure 15). Only single estimates are available for the relation between egg concentration and chick survival, so exposure-response curves cannot be developed (Figure 16).

The field-exposure study performed with feed containing variable proportions of Saginaw Bay carp (Summer, et al. 1996) is shown as "PCB" in the figures. All other studies used commercial Aroclors. The Saginaw data are included for comparative purposes and are not used for deriving TRVs.

The original data used for calculating relative responses and their sources are documented in a separate spreadsheet titled "Summary of Chicken PCB Studies and Relative Responses" (PCB chick RR.123).

Literature Cited

Klemm, D., G. Morrison, T. Norberg-King, W. Peltier, and M. Heber. 1994. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms, 2nd ed. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA/600/4-91/003.

Leonards, P., T. de Vries, W. Minnaard, S. Stuijfzand, P. de Voogt, W. Cofino, N. van Straalen and B. van Hattum. 1995. Assessment of experimental data on PCB-induced reproduction inhibition in mink, based on an isomer- and congener-specific approach using 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalency. Environ Toxicol Chem 14: 639-652.

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[2] One modification is that the interpolation is performed with the base 10 logarithm of the dose or concentration. This is done because most of the responses are linear against the logarithm of the dose or egg concentration (see figures). Another modification is that no adjustment is made when treatment responses exceed control responses, since the recommended procedure applies to the results of a single study, not the multiple studies used here. Note that there are errors in the Appendix L example calculation in Klemm, et al. (1994).

Medway, W. and M. Kare. 1959. Water metabolism of the growing domestic fowl with special reference to water balance. Poultry Sci 38: 631-637. as cited in USEPA. 1995. Great Lakes Water Quality Initiative Criteria Documents for the Protection of Wildlife: DDT, Mercury, 2,3,7,8-TCDD, PCBs. Office of Water. EPA-820-B-95-008.

Platonow, N. and B. Reinhart. 1973. The effects of polychlorinated biphenyls Aroclor 1254 on chicken egg production fertility and hatchability. Can J Comp Med 37: 341-346.

Sotherland, P. and H. Rahn. 1987. On the composition of bird eggs. Condor 89: 48-65. as cited in Hoffman, D., C. Rice, and T. Kubiak. 1996. PCBs and dioxins in birds. *In* Environmental Contaminants in Wildlife, Interpreting Tissue Concentrations. (W. Beyer, G. Heinz and A. Redmon-Norwood, eds.). Lewis, Boca Raton. pp. 165-207.

Summer, C., J. Giesy, S. Bursian, J. Render, T. Kubiak, P. Jones, D. Verbrugge, and R. Aulerich. 1996a. Effects induced by feeding organochlorine-contaminated carp from Saginaw Bay, Lake Huron, to laying white leghorn hens. I. Effects on health of adult hens, egg production, and fertility. J Toxicol Environ Health 49: 389-407.

Summer, C., J. Giesy, S. Bursian, J. Render, T. Kubiak, P. Jones, D. Verbrugge, and R. Aulerich. 1996b. Effects induced by feeding organochlorine-contaminated carp from Saginaw Bay, Lake Huron, to laying white leghorn hens. II. Embryotoxic and teratogenic effects. J Toxicol Environ Health 49: 409-438.

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John Giesy, Michigan State University, Entrix
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Figure 1. Hatchability vs. Dose to Chicken Hens

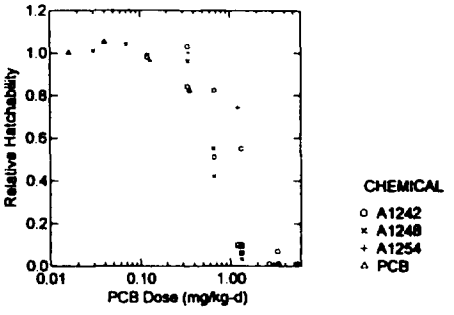


Figure 2. Hatchability vs. A1242 Dose to Hens

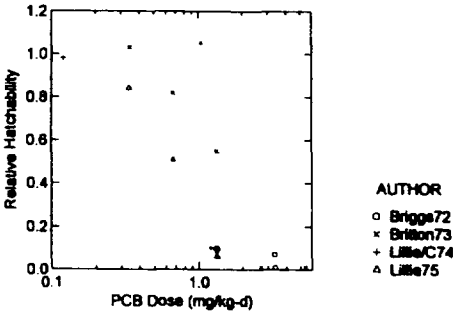


Figure 3. Hatchability vs. A1248 Dose to Hens

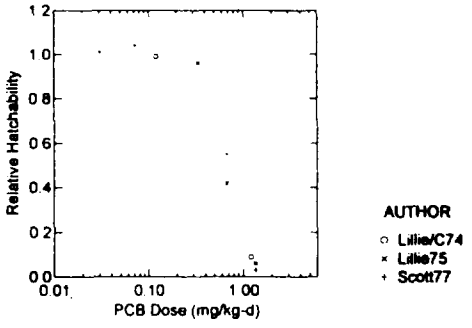
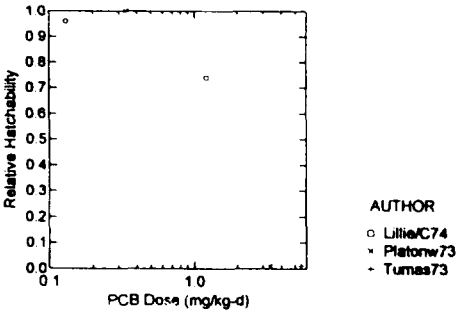


Figure 4. Hatchability vs. A1254 Dose to Hens



Author is lead author and date. See notes to Table 2 for citations.

Figure 5. Hatchability vs Egg Residue

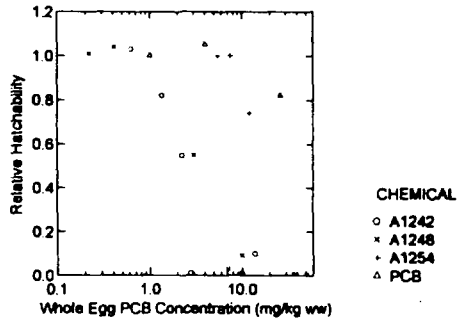


Figure 6. Hatchability vs A1242 Egg Residue

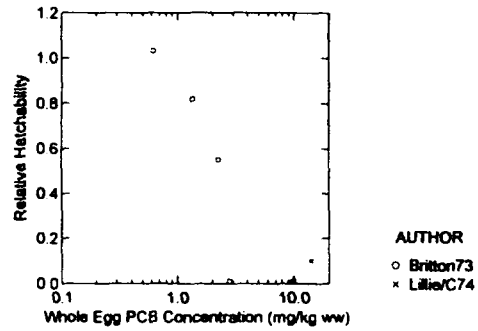


Figure 7. Hatchability vs A1248 Egg Residue

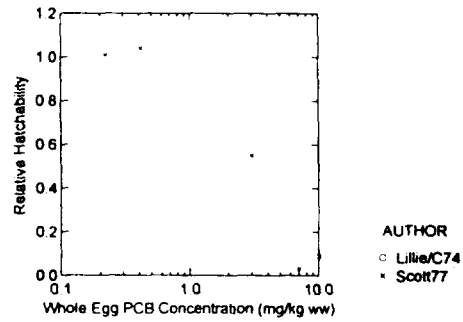


Figure 8. Hatchability vs A1254 Egg Residue

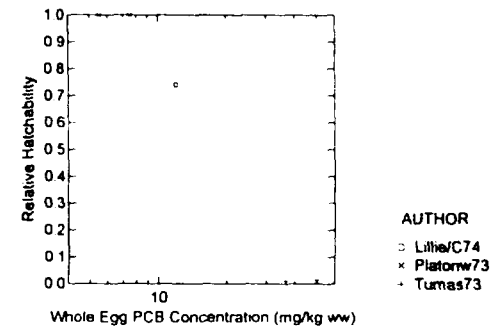


Figure 9. Chick Bodyweight vs Dose to Hens

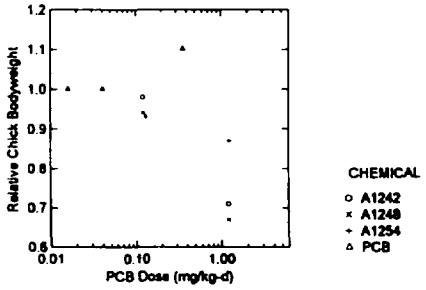


Figure 10. Chick Bodyweight vs Egg Residue

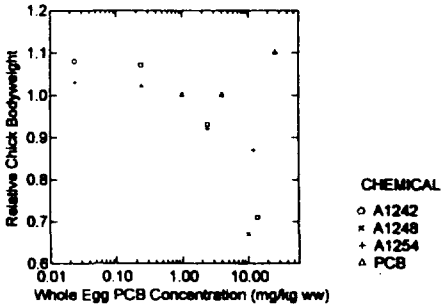


Figure 11. Chick BW vs A1242 Egg Residue

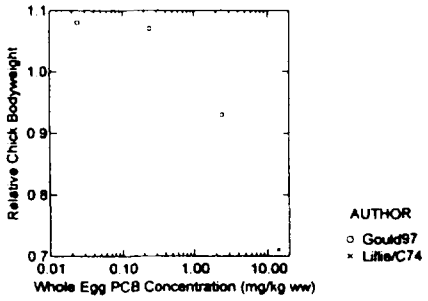


Figure 12. Chick Survival vs. Dose to Hens

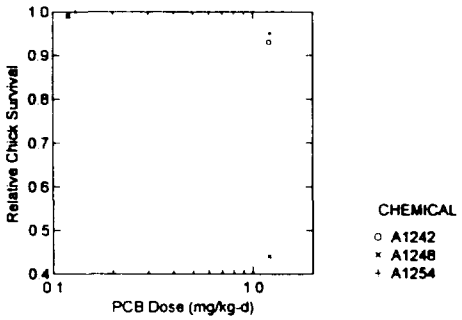


Figure 13. Egg Productivity vs. Dose to Hens

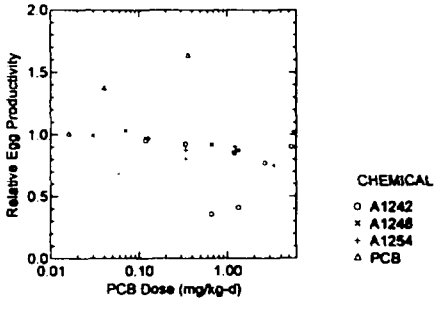


Figure 14. Egg Fertility vs. Dose to Hens

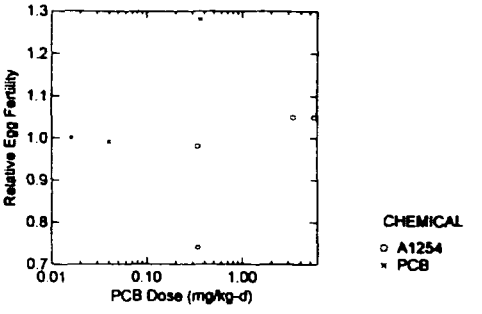


Figure 15. Chick Normality vs. Dose to Hens

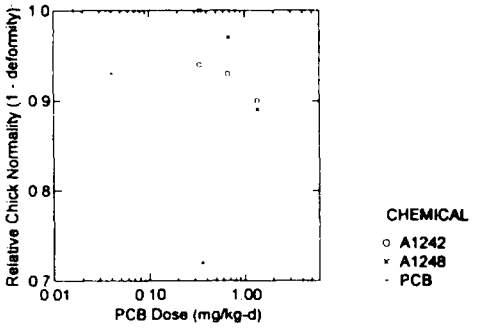


Figure 16. Chick Survival vs. Egg Residue

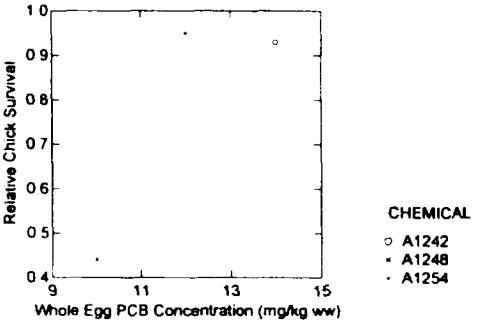


Table 1. Log-Linear Interpolation of PCB Toxicity Reference Values (TRV) for Chicken

Chemical	Response	Control	Treatment dose < TRV		Treatment dose > TRV		Target	TRV	Effect level	Study
		RR	dose	RR	dose	RR	RR			
		M_1	D_j	M_j	D_{j+1}	M_{j+1}	P			
Hen Dose (mg/kg_{BW}-d)										
A1242	hatchability	1	0.67	0.82	1.34	0.55	0.75	0.80	low effect	Britton73
A1242	hatchability	1	0.34	1.03	0.67	0.82	1	0.37	no effect	Britton73
A1242	hatchability	1	0.34	0.84	0.67	0.51	0.75	0.41	low effect	Lillie75
A1242	hatchability	1	0.12	0.98			1	0.12	no effect	Lillie/Cecil74
A1242	chick bw	1	0.12	0.98	1.21	0.71	0.75	0.86	low effect	Lillie/Cecil74
A1242	chick bw	1	0.12	0.98			1	0.12	no effect	Lillie/Cecil74
A1248	hatchability	1	0.34	0.96	0.67	0.55	0.75	0.48	low effect	Lillie75; Scott77
A1248	hatchability	1	0.12	0.99			1	0.12	no effect	Lillie/Cecil74
A1248	chick bw	1	0.12	0.94	1.21	0.67	0.75	0.61	low effect	Lillie/Cecil74
A1248	chick bw	1	0.12	0.94			1	0.12	no effect	Lillie/Cecil74
A1248	survival	1	0.12	0.99	1.21	0.44	0.75	0.33	low effect	Lillie/Cecil74
A1248	survival	1	0.12	0.99			1	0.12	no effect	Lillie/Cecil74
A1254	hatchability	1	0.34	1	1.22	0.74	0.75	1.16	low effect	Platonw73; Lillie/Cecil74
A1254	hatchability	1	0.34	1			1	0.34	no effect	Platonw73
Egg Concentration (mg/kg, ww)			conc		conc					
		M_1	C_j	M_j	C_{j+1}	M_{j+1}	P	TRV	Effect level	Study
A1242	hatchability	1	1.35	0.82	2.26	0.55	0.75	1.54	low effect	Britton73
A1242	hatchability	1	0.62	1.03	1.35	0.82	1	0.69	no effect	Britton73
A1242	chick bw	1	2.44	0.93	14	0.71	0.75	10.19	low effect	Gould97; Lillie/Cecil74
A1242	chick bw	1	0.24	1.07	2.44	0.93	1	0.77	no effect	Gould97
A1248	hatchability	1	0.41	1.04	3	0.55	0.75	1.33	low effect	Scott77
A1248	hatchability	1	0.41	1.04	3	0.55	1	0.48	no effect	Scott77
A1254	hatchability	1	7.5	1	12	0.74	0.75	11.79	low effect	Platonw73; Lillie/Cecil74
A1254	hatchability	1	7.5	1			1	7.5	no effect	Platonw73

Notes for Table 1.

bw - bodyweight
conc - whole egg PCB concentration, mg/kg, ww
dose - bodyweight-normalized ingestion, mg PCB/kg_{BW}-d
RR - relative response = treatment response / control response
Study - lead author, date; see notes for Table 2 for citations
TRV - toxicity reference value for PCB dose (D) (mg/kg_{BW}-d) or whole egg concentration (C) (mg/kg wet weight (ww))

$$\text{Log}_{10}\,TRV = \text{Log}_{10}\,D_j + (((M_1 * P) - M_j) * ((\text{Log}_{10}\,D_{j+1} - \text{Log}_{10}\,D_j) / (M_{j+1} - M_j)))$$

$$\text{Log}_{10}\,TRV = \text{Log}_{10}\,C_j + (((M_1 * P) - M_j) * ((\text{Log}_{10}\,C_{j+1} - \text{Log}_{10}\,C_j) / (M_{j+1} - M_j)))$$

$$TRV = 10^{\text{Log}10\,TRV}$$

Table 2. Chicken PCB Toxicity Studies

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
1	A1242 product	chicken (white leghorn)	6 wk	1.34				0.10, 6 wk			
				3.35				0, 6 wk			
		chicken (broiler)		1.34				0.09, 6 wk			
				3.35				0.07, 6 wk			
2	A1242 product	chicken (white leghorn)	6 wk	0.34 (control NA)	0.62 ppm 6 wk	0.92, 6 wk		1.03, 6 wk			
				0.67	1.35 ppm 6 wk	0.36 6 wk		0.82 6 wk			
				1.34	2.26 ppm 6 wk	0.41 6 wk		0.55 6 wk			
				2.68	2.8 ppm 6 wk	0.77 6 wk		0 6 wk			
				5.36	10.01 ppm 6 wk	0.90 6 wk		0 6 wk			
3	A1254 product	chicken (white leghorn)	14 wk	0.34 (control NA)	5.5 ppm (max.) 2-14 wk	0.87 1-14 wk	0.98 1-14 wk	1 1-14 wk			
			39 wk	0.34	7.5 ppm (max.) 26-35 wk	0.80 26-39 wk	0.74 34-39 wk	1 1-39 wk			

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
			14 wk	3.35	50 ppm (max.) 2-14 wk	0.75 1-14 wk	1.05 1-14 wk	0 3-6 wk			
4	A1254 product	chicken (white leghorn)	6 wk	5.5 (control NA)	10 ppm 1 wk; 24 ppm 2 wk; 36.4 ppm 3 wk; (control NA)	1.02 1-6 wk	1.05 1-6 wk	0.41 2 wk; 0 3-6 wk			
5	A1221 product	chicken (white leghorn)	9 wk	1.30 (control NA)	<1 ppm 9 wk	1 0-9 wk		0.99 0-9 wk	0.98 6-9 wk	1	
	A1232 product			1.34	2.5 ppm 9 wk	0.91 0-9 wk		0.60 0-9 wk 0.43 8 wk	0.85 6-9 wk	0.93	
	A1242 product			0.12		0.95 0-9 wk		0.98 0-9 wk	0.98 6-9 wk	0.99	
				1.21	14 ppm 9 wk	0.85 0-9 wk		0.20 0-9 wk 0.10 8 wk	0.71 6-9 wk	0.93	
	A1248 product			0.12		0.97 0-9 wk		0.99 0-9 wk	0.94 6-9 wk	0.99	

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
				1.21	10 ppm 9 wk	0.85 0-9 wk		0.13 0-9 wk 0.09 8 wk	0.67 6-9 wk	0.44	
	A1254 product			0.13		0.97 0-9 wk		0.96 0-9 wk	0.93 6-9 wk	1	
				1.22	12 ppm	0.90 0-9 wk		0.86 0-9 wk 0.74 8 wk	0.87 6-9 wk	0.95	
	A1268 product			1.28	23 ppm	0.94 0-9 wk		0.98 0-9 wk	0.96 6-9 wk	1	
6	A1232 product	chicken (white leghorn)	8 wk	0.67 (control NA)				0.86 8 wk			
				1.34				0.57, 8 wk			
	A1242 product			0.34				0.84, 0-8 wk			0.94
				0.67				0.74, 0-8 wk 0.51, 8 wk			0.93
				1.34				0.31, 0-8 wk 0.06, 8 wk			0.90
	A1248 product			0.34				0.96, 0-8 wk			1
				0.67				0.75, 0-8 wk 0.42, 8 wk			0.97

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
				1.34				0.24, 0-8 wk 0.06, 8 wk			0.89
7	A1248 product	chicken (white leghorn)	8 wk	0.03 (control NA)	0.16 ppm 4 wk; 0.22 ppm 8 wk	0.99 8 wk		1.01 4 wk 1.01 8 wk			
				0.07	0.33 ppm 4 wk; 0.41 ppm 8 wk	1.03 8 wk		0.98 4 wk 1.04 8 wk			
				0.67	2.2 ppm 4 wk; 3 ppm 8 wk	0.92 8 wk		0.73 4 wk 0.55 8 wk			
				1.34	4.5 ppm 4 wk; 7 ppm 8 wk	0.87 8 wk		0.03 4 wk 0.03 8 wk			
8	reported as A1242, 1248, 1254 and 1260; H4IIE bioassay TEQ; Saginaw Bay carp	chicken (white leghorn)	8 wk	PCB 0.04 (control 0.016); TEQ 1.4 ng/kg-d (control 0.2)	4 ppm 4-8 wk (control 1 ppm)	1.37 4-8 wk	0.99 4-8 wk	1.05 4-8 wk	1.0 hatch		0.93 -1 to 8 wk

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
				PCB 0.36; TEQ 3.2	26 ppm 4-8 wk	1.63 4-8 wk	1.28 4-8 wk	0.82 4-8 wk	1.1 hatch		0.72 -1 to 8 wk
9	A1242 product	chicken eggs (white leghorn)	injected in yolk		0.02 ppm (control NA)				1.08 embryo		
					0.24 ppm				1.07 embryo		
					2.44 ppm				0.93 embryo		
	A1254 product				0.02 ppm				1.03 embryo		
					0.24 ppm				1.02 embryo		
					2.44 ppm				0.92 embryo		

Notes for Table 2.

Ref - references [abbreviated reference used in the figures and Table 1 in brackets]:

1) [Briggs72] Briggs, D. and J. Harris. 1972. Polychlorinated biphenyls influence on hatchability. Poultry Sci 52: 1291-1294.

2) [Britton73] Britton, W. and T. Huston. 1973. Influence of polychlorinated biphenyls in the laying hen. Poultry Sci 52: 1620-1624.

3) [Platonw73] Platonow, N. and B. Reinhart. 1973. The effects of polychlorinated biphenyls Aroclor 1254 on chicken egg production fertility and hatchability. Can J Comp Med 37: 341-346.

4) [Tumas73] Tumasonis, C., B. Bush, and F. Baker. 1973. PCB levels in egg yolks associated with embryonic mortality and deformity of hatched chicks. Arch Environ Contam Toxicol 1: 312-324.

5) [Lillie/Cecil74 or Lillie/C74] Lillie, R., H. Cecil, J. Bitman, and G. Fries. 1974. Differences in response of caged white leghorn layers to various polychlorinated biphenyls (PCBs) in the diet. Poultry Sci 53: 726-732; Cecil, H., J. Bitman, R. Lillie, G. Fries, and J. Verrett. 1974. Embryotoxic and teratogenic effects in unhatched fertile eggs from hens fed polychlorinated biphenyls (PCBs). Bull Environ Contam Toxicol 11: 489-495.

6) [Lillie75] Lillie, R., H. Cecil, J. Bitman, G. Fries, and J. Verrett. 1975. Toxicity of certain polychlorinated and polybrominated biphenyls on reproductive efficiency of caged chickens. Poultry Sci 54: 1550-1555.

7) [Scott77] Scott, M. 1977. Effects of PCBs, DDT and mercury compounds in chickens and Japanese quail. Fed Proceed 36: 1888-1893.

8) [Summer96] Summer, C., J. Giesy, S. Bursian, J. Render, T. Kubiak, P. Jones, D. Verbrugge, and R. Aulerich. 1996a. Effects induced by feeding organochlorine-contaminated carp from Saginaw Bay, Lake Huron, to laying white leghorn hens. I. Effects on health of adult hens, egg production, and fertility. J Toxicol Environ Health 49: 389-407; Summer, C., J. Giesy, S. Bursian, J. Render, T. Kubiak, P. Jones, D. Verbrugge, and R. Aulerich. 1996b. Effects induced by feeding organochlorine-contaminated carp from Saginaw Bay, Lake Huron, to laying white leghorn hens. II. Embryotoxic and teratogenic effects. J Toxicol Environ Health 49: 409-438. Weeks represent time from onset of exposure in contrast to the original publications in which the number of weeks include a 2-wk acclimation period prior to PCB exposure.

9) [Gould97] Gould, J., K. Cooper, C. Scanes. 1997. Effects of polychlorinated biphenyl mixtures and three specific congeners on growth and circulating growth-related hormones. Gen Compar Endrocrinol 106: 221-230.

Exposures occur through contaminated feed except for Tumasonis, et al. (1973) through contaminated water, and Gould, et al. (1997) through yolk injection.

Relative Response Compared to Control = treatment response / control response

Source: product is commercial product mixed with feed or in water; field is field-contaminated biota prepared as feed

Dose: Calculated from experimental data when available. Generic calculation based on a white leghorn hen food ingestion rate of 0.067 kg feed/kg_{BW}-d (Medway and Kare 1959 cited in USEPA 1995).

Egg Concentration: Yolk concentration is converted to whole-egg concentration by multiplying by 0.364 (Southerland and Rahn 1987 as cited in Hoffman, et al. 1996).

Chick normality is the proportion of chicks without deformities (= 1 - deformity rate)

Lead author Date	Chemical	Dietary conc. mg/kg fw	Food ingestion kg/kgbw fw	Dose mg/kg-d	Exposure duration wk	Yolk conc. mg/kg fw	Whole egg conc. mg/kg fw	Egg conc. source	Control # or %	Productivity Treatment # or %	RR ratio	Productivity source	Control %	Fertility Treatment %	RR ratio	Fertility source
Briggs72	A1242	20	0.067	1.34	6											
Briggs72	A1242	50	0.067	3.35	6											
Briggs72	A1242	20	0.067	1.34	6											
Briggs72	A1242	50	0.067	3.35	6											
Britton73	A1242	5	0.067	0.34	6	1.7	0.62	table 3 wk 6	61	56	0.92	table 1 wk 6				
Britton73	A1242	10	0.067	0.67	6	3.7	1.35	table 3 wk 6	61	22	0.36	table 1 wk 6				
Britton73	A1242	20	0.067	1.34	6	6.2	2.26	table 3 wk 6	61	25	0.41	table 1 wk 6				
Britton73	A1242	40	0.067	2.68	6	7.7	2.80	table 3 wk 6	61	47	0.77	table 1 wk 6				
Britton73	A1242	80	0.067	5.36	6	27.5	10.01	table 3 wk 6	61	55	0.90	table 1 wk 6				
Platonw73	A1254	5	0.067	0.34	14		5.5	fig 4 max. wk 12	82.7	72	0.87	text p 343 wk 1-14	85.5	83.6	0.98	text p 344 wk 1-14
Platonw73	A1254	5	0.067	0.34	39		7.5	fig 4 max. wk 26	72	57.5	0.80	text p 343 wk 26-3	85	63.3	0.74	fig 2 wk 34-39
Platonw73	A1254	50	0.067	3.35	14		50	fig 4 max. wk 12	82.7	62.2	0.75	text p 343 wk 1-14	85.5	89.9	1.05	text p 344 wk 1-14
Tumas73	A1254	50	0.11	5.50	6	100	36.40	fig 2 wk 3	8.6	8.77	1.02	table 1 wk 1-6	92.3	97.2	1.05	table 1 wk 1-6
Lillie/Cecil74	A1221	20	0.0649	1.30	9		<1	Cecil fig 4 wk 9	79.4	79.3	1.00	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1232	20	0.067	1.34	9		2.5	Cecil fig 4 wk 9	79.4	71.9	0.91	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1242	2	0.0615	0.12	9				79.4	75.5	0.95	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1242	20	0.0605	1.21	9		14	Cecil fig 4 wk 9	79.4	67.5	0.85	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1248	2	0.0623	0.12	9				79.4	76.9	0.97	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1248	20	0.0607	1.21	9		10	Cecil fig 4 wk 9	79.4	67.5	0.85	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1254	2	0.0636	0.13	9				79.4	77.1	0.97	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1254	20	0.061	1.22	9		12	Cecil fig 4 wk 9	79.4	71.3	0.90	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1268	20	0.0641	1.28	9		23	Cecil fig 4 wk 9	79.4	74.4	0.94	Lillie table 1 wk 0-9				
Lillie75	A1232	10	0.067	0.67	8											
Lillie75	A1232	20	0.067	1.34	8											
Lillie75	A1242	5	0.067	0.34	8											
Lillie75	A1242	10	0.067	0.67	8											
Lillie75	A1242	20	0.067	1.34	8											
Lillie75	A1248	5	0.067	0.34	8											
Lillie75	A1248	10	0.067	0.67	8											
Lillie75	A1248	20	0.067	1.34	8											
Scott77	A1248	0.5	0.067	0.03	8		0.22	table 1 wk 8	74.5	74	0.99	table 3 wk 8				
Scott77	A1248	1	0.067	0.07	8		0.41	table 1 wk 8	74.5	76.6	1.03	table 3 wk 8				
Scott77	A1248	10	0.067	0.67	8		3	table 1 wk 8	74.5	68.7	0.92	table 3 wk 8				
Scott77	A1248	20	0.067	1.34	8		7	table 1 wk 8	74.5	64.8	0.87	table 3 wk 8				
Summer96	PCB	0.8	0.0553	0.04	8		4	96b table 1 wk 6-1	54	74	1.37	96a table 5 wk 6-1	67	66.6	0.99	96a table 6 wk 6-1
Summer96	PCB	6.6	0.0548	0.36	8		26	96b table 1 wk 6-1	54	88	1.63	96a table 5 wk 6-1	67	85.7	1.28	96a table 6 wk 6-1
Gould97	A1242	yolk inject				0.067	0.02	table 1								
Gould97	A1242	yolk inject				0.67	0.24	table 1								
Gould97	A1242	yolk inject				6.7	2.44	table 1								
Gould97	A1254	yolk inject				0.067	0.02	table 1								
Gould97	A1254	yolk inject				0.67	0.24	table 1								
Gould97	A1254	yolk inject				6.7	2.44	table 1								

Notes:
Default Food ingestion rate - 0.067 kg feed/kgbw-d white leghorn hen (Medway and Kare 1959)
Whole egg conc. = 0.364 yolk conc. (Southerland and Rahn 1987)
RR - relative response = treatment response / control response; Normality = 1 - deformity
Tumas73 - Dietary conc. is mg/l water conc; Food ingestion rate is l/kgbw-d water ingestion = 0.177 l/hen/d / 1.61 kgbw/hen (p. 314, 315)
Lillie/Cecil74 - Food consumption = treatment food/hen-d (Lillie table 2 wk 0-9) / 1.953 kg mean initial hen bodyweight (Lillie p 727)
Lillie75 - Normality = 1 - abnormal embryos as % of fertile eggs
Summer96 - Food ingestion rate - mean for wk 3-10 (96a table 4); Chick deformity recalculated from 96b table 5 (replace rounded percentages)
Gould97 - Yolk injection on day 0 of incubation. Treatment "chick" bodyweight is % difference in 17-d embryo bodyweight compared to control

Lead author Date	Chemical	Dietary conc. mg/kg fw	Control %	Hatchability Treatment %	RR ratio	Hatchability source	Chick Bodyweight Control g	Treatment g	RR ratio	Bodyweight source	Chick Survival Control %	Treatment %	RR ratio	Survival source	hick Normality (1 - defomity Control %	Treatment %	RR ratio
Briggs72	A1242	20	68.9	7.2	0.10	table 1 wk 6 leghorn											
Briggs72	A1242	50	68.9	0	0.00	table 1 wk 6 leghorn											
Briggs72	A1242	20	65.5	6.2	0.09	table 1 wk 6 broiler											
Briggs72	A1242	50	65.5	4.5	0.07	table 1 wk 6 broiler											
Britton73	A1242	5	91	94	1.03	table 3 wk 6											
Britton73	A1242	10	91	75	0.82	table 3 wk 6											
Britton73	A1242	20	91	50	0.55	table 3 wk 6											
Britton73	A1242	40	91	0	0.00	table 3 wk 6											
Britton73	A1242	80	91	0	0.00	table 3 wk 6											
Platonw73	A1254	5	90	90	1.00	text p 344 wk 1-14											
Platonw73	A1254	5	90	90	1.00	text p 344, wk 1-39											
Platonw73	A1254	50	90	0	0.00	text p 344 wk 2-14											
Tumas73	A1254	50	84.7	0	0.00	table 1 wk 3-6											
Lillie/Cecil74	A1221	20	93.7	93.2	0.99	Lillie table 3 wk 0-9	163	159	0.98	Lillie table 4 wk 6-	98.4	98.3	1.00	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1232	20	92.4	40	0.43	Cecil fig 1 wk 8	163	139	0.85	Lillie table 4 wk 6-	98.4	91.9	0.93	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1242	2	93.7	92.2	0.98	Lillie table 3 wk 0-9	163	160	0.98	Lillie table 4 wk 6-	98.4	97.1	0.99	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1242	20	92.4	9	0.10	Cecil fig 1 wk 8	163	115	0.71	Lillie table 4 wk 6-	98.4	91.7	0.93	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1248	2	93.7	92.3	0.99	Lillie table 3 wk 0-9	163	153	0.94	Lillie table 4 wk 6-	98.4	97.5	0.99	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1248	20	92.4	8	0.09	Cecil fig 1 wk 8	163	109	0.67	Lillie table 4 wk 6-	98.4	43.7	0.44	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1254	2	93.7	89.7	0.96	Lillie table 3 wk 0-9	163	151	0.93	Lillie table 4 wk 6-	98.4	98.7	1.00	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1254	20	92.4	68	0.74	Cecil fig 1 wk 8	163	141	0.87	Lillie table 4 wk 6-	98.4	93.7	0.95	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1268	20	93.7	92.2	0.98	Lillie table 3 wk 0-9	163	156	0.96	Lillie table 4 wk 6-	98.4	98.7	1.00	Lillie table 4 wk 6-9			
Lillie75	A1232	10	90	77	0.86	text p 1554 wk 8											
Lillie75	A1232	20	90	51	0.57	text p 1554 wk 8											
Lillie75	A1242	5	91	76	0.84	table 3 wk 4-8									98	92	0.94
Lillie75	A1242	10	90	46	0.51	text p 1554 wk 8									98	91	0.93
Lillie75	A1242	20	90	5	0.06	text p 1554 wk 8									98	88	0.90
Lillie75	A1248	5	91	87	0.96	table 3 wk 4-8									98	98	1.00
Lillie75	A1248	10	90	38	0.42	text p 1554 wk 8									98	95	0.97
Lillie75	A1248	20	90	5	0.06	text p 1554 wk 8									98	87	0.89
Scott77	A1248	0.5	90.5	91.6	1.01	table 4 wk 8											
Scott77	A1248	1	90.5	93.7	1.04	table 4 wk 8											
Scott77	A1248	10	90.5	50	0.55	table 4 wk 8											
Scott77	A1248	20	90.5	2.4	0.03	table 4 wk 8											
Summer96	PCB	0.8	85.8	90	1.05	96b table 2 wk 6-1	34.49	34.49	1.00	96b table 4 wk 6-10					82.7	76.5	0.93
Summer96	PCB	6.6	85.8	70.2	0.82	96b table 2 wk 6-1	34.49	37.81	1.10	96b table 4 wk 6-10					82.7	59.9	0.72
Gould97	A1242	yolk inject						+8.4 %	1.08	fig 2 (17-d embryo)							
Gould97	A1242	yolk inject						+6.7 %	1.07	fig 2 (17-d embryo)							
Gould97	A1242	yolk inject						-7.0 %	0.93	fig 2 (17-d embryo)							
Gould97	A1254	yolk inject						+2.8 %	1.03	fig 2 (17-d embryo)							
Gould97	A1254	yolk inject						+2.1 %	1.02	fig 2 (17-d embryo)							
Gould97	A1254	yolk inject						-7.7 %	0.92	fig 2 (17-d embryo)							

Lead author Date	Chemical	Dietary conc. mg/kg fw	Normality source
Briggs72	A1242	20	
Briggs72	A1242	50	
Briggs72	A1242	20	
Briggs72	A1242	50	
Britton73	A1242	5	
Britton73	A1242	10	
Britton73	A1242	20	
Britton73	A1242	40	
Britton73	A1242	80	
Platonw73	A1254	5	
Platonw73	A1254	5	
Platonw73	A1254	50	
Tumas73	A1254	50	
Lillie/Cecil74	A1221	20	
Lillie/Cecil74	A1232	20	
Lillie/Cecil74	A1242	2	
Lillie/Cecil74	A1242	20	
Lillie/Cecil74	A1248	2	
Lillie/Cecil74	A1248	20	
Lillie/Cecil74	A1254	2	
Lillie/Cecil74	A1254	20	
Lillie/Cecil74	A1268	20	
Lillie75	A1232	10	
Lillie75	A1232	20	
Lillie75	A1242	5	Table 3 wk 4-8
Lillie75	A1242	10	Table 3 wk 4-8
Lillie75	A1242	20	Table 3 wk 4-8
Lillie75	A1248	5	Table 3 wk 4-8
Lillie75	A1248	10	Table 3 wk 4-8
Lillie75	A1248	20	Table 3 wk 4-8
Scott77	A1248	0.5	
Scott77	A1248	1	
Scott77	A1248	10	
Scott77	A1248	20	
Summer96	PCB	0.8	96b table 5 wk 1-10
Summer96	PCB	6.6	96b table 5 wk 1-10
Gould97	A1242	yolk inject	
Gould97	A1242	yolk inject	
Gould97	A1242	yolk inject	
Gould97	A1254	yolk inject	
Gould97	A1254	yolk inject	
Gould97	A1254	yolk inject	

PCB chicken graph file.123

AUTHOR$	CHEMICAL$	SOURCE$	SPECIES$	PCBDOSE	DURATION	EGGCONC	PRODUCTI	FERTILITY	HATCHABIL	CHICKBW	SURVIVAL	NORMALITY
Briggs72	A1242	product	chicken	1.34	6				0.1			
Briggs72	A1242	product	chicken	3.35	6				0.01			
Briggs72	A1242	product	chicken	1.34	6				0.09			
Briggs72	A1242	product	chicken	3.35	6				0.07			
Britton73	A1242	product	chicken	0.34	6	0.62	0.92		1.03			
Britton73	A1242	product	chicken	0.67	6	1.35	0.36		0.82			
Britton73	A1242	product	chicken	1.34	6	2.26	0.41		0.55			
Britton73	A1242	product	chicken	2.68	6	2.8	0.77		0.01			
Britton73	A1242	product	chicken	5.36	6	10.01	0.9		0.01			
Platonw73	A1254	product	chicken	0.34	14	5.5	0.87	0.98	1			
Platonw73	A1254	product	chicken	0.34	39	7.5	0.8	0.74	1			
Platonw73	A1254	product	chicken	3.35	14	50	0.75	1.05	0.01			
Tumas73	A1254	product	chicken	5.5	6	36.4	1.02	1.05	0.01			
Lillie/C74	A1242	product	chicken	0.12	9		0.95		0.98	0.98	0.99	
Lillie/C74	A1242	product	chicken	1.21	9	14	0.85		0.1	0.71	0.93	
Lillie/C74	A1248	product	chicken	0.12	9		0.97		0.99	0.94	0.99	
Lillie/C74	A1248	product	chicken	1.21	9	10	0.85		0.09	0.67	0.44	
Lillie/C74	A1254	product	chicken	0.13	9		0.97		0.96	0.93	1	
Lillie/C74	A1254	product	chicken	1.22	9	12	0.9		0.74	0.87	0.95	
Lillie75	A1242	product	chicken	0.34	8				0.84			0.94
Lillie75	A1242	product	chicken	0.67	8				0.51			0.93
Lillie75	A1242	product	chicken	1.34	8				0.06			0.9
Lillie75	A1248	product	chicken	0.34	8				0.96			1
Lillie75	A1248	product	chicken	0.67	8				0.42			0.97
Lillie75	A1248	product	chicken	1.34	8				0.06			0.89
Scott77	A1248	product	chicken	0.03	8	0.22	0.99		1.01			
Scott77	A1248	product	chicken	0.07	8	0.41	1.03		1.04			
Scott77	A1248	product	chicken	0.67	8	3	0.92		0.55			
Scott77	A1248	product	chicken	1.34	8	7	0.87		0.03			
Summer96	PCB	field	chicken	0.016	8	1	1	1	1	1		1
Summer96	PCB	field	chicken	0.04	8	4	1.37	0.99	1.05	1		0.93
Summer96	PCB	field	chicken	0.36	8	26	1.63	1.28	0.82	1.1		0.72
Gould97	A1242	product	chicken			0.024				1.08		
Gould97	A1242	product	chicken			0.24				1.07		
Gould97	A1242	product	chicken			2.44				0.93		
Gould97	A1254	product	chicken			0.024				1.03		
Gould97	A1254	product	chicken			0.24				1.02		
Gould97	A1254	product	chicken			2.44				0.92		

Responses to Peer Review Comments
Wildlife PCB Toxicity Reference Values

March 6, 2003

U.S. Environmental Protection Agency
Region 5
Superfund Division
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Table of Contents

List of Figures

1. Introduction

This memo presents the results of an internal USEPA peer review of the development of PCB toxicity reference values (TRVs) for wildlife. The TRVs are interpolated from dose-response plots of combined studies in which a sensitive species (mink or chicken) was exposed to commercial PCB products in captivity. TRVs are developed separately for selected Aroclors. This memo includes the peer review charge, panel members, consolidated comments, and responses.

2. Peer Review Charge for Mink and Chicken PCB Toxicity Reference Values Derived Through an EDx (Effective Dose) Procedure

Background

Continuing Need for Aroclor-based TRVs

Although congener-specific analyses are recommended for assessing risks to PCBs, Aroclor-based toxicity reference values (TRVs) are still needed for several reasons. 1) The PCB database at many sites is predominantly or solely Aroclor data. This is especially true of historic data. 2) At contentious sites, the lengthy process for resolving disagreements has resulted in a need to finalize Aroclor-based risk assessments initiated prior to the current emphasis on congener-based approaches. In these situations, abandonment of the an Aroclor approach will entail substantial delay and cost for resampling media and biota to provide synoptic congener data. 3) There is a larger database available on the ecotoxicological effects of PCBs on an Aroclor basis as compared to a dioxin toxic equivalent (TEQ) basis. 4) The utility of the TEQ-based ecotoxicological studies is also compromised by the use of inconsistent toxic equivalency factors (TEF). Conversion to a common TEQ basis is feasible only if the original congener data is reported so that the TEF scheme of choice can be applied, but the underlying congener data are rarely reported in journal articles–further reducing the pool of useable TEQ studies. Studies based on bioassay TEQs, such as the HII4E rat hepatoma cell line, cannot be directly compared to calculated TEQs, and the bioassay results vary with the choice of solvent for dosing the cells. 5) The key premise of the TEQ approach is that the effects of PCBs are primarily due to aryl hydrocarbon receptor (AhR)-mediated processes (dioxin-like effects). Although AhR-mediated effects are frequently reported to be more sensitive endpoints compared to non-AhR effects, it is not clear how generally this relationship applies across taxa and endpoints. In the absence of a non-AhR TEF scheme, an Aroclor-based assessment can provide an indication whether significant non-AhR effects may have been missed in a TEQ-based assessment.

One of the criticisms of Aroclor-based assessments is that the results are more variable compared to TEQ-based assessments. However, in one such comparison by Leonards, et al. (1995), no distinction was made between different Aroclors or Clophens (total PCB vs. reproductive effects in mink was unfavorably compared to TEQ vs. reproductive effects). This comparison was biased since different Aroclors or Clophens differ in their toxicity.

NOAEL/LOAEL Approach

A widely used approach for determining TRVs depends on two statistically-based thresholds: the no observed adverse effect level (NOAEL), which is the highest dose tested that did not result in a statistically discernible effect compared to the control, and the lowest observed adverse effect level (LOAEL), which is the lowest dose that resulted in a statistically discernible adverse effect. Shortcomings in this approach have been long recognized–the main one is that the NOAEL and LOAEL are affected by factors unrelated to toxicity. An obvious factor is that the TRVs can only be selected from the particular doses used in an experiment (commonly the tested doses are an order of magnitude apart so there are large gaps in the data). Second, statistical significance is not solely determined by toxicity, but also by the statistical power of the study. This has two implications: 1) studies performed with low statistical power will result in higher TRVs compared with studies with high statistical power for the same chemical and receptor, and 2) since the TRVs are statistically defined, the level of adverse effects associated with the NOAEL or LOAEL varies greatly between studies (for example, statistically-derived NOAELs may be associated with adverse effects in as much as 50 % of the test organisms). A related consideration is that this approach acts as a disincentive for improving the quality and statistical power of industry-funded toxicological testing since less rigorous studies are less expensive and have low statistical power that results in higher and less protective TRVs.

EDx or ECx Approach

An alternative is to use the data from toxicological studies to develop dose- or exposure-response relationships, and to use the relationships to determine the no-effect and low-effect doses or exposures that correspond to selected effect levels. This frees the analysis from the specific doses used in a study (a TRV can now be interpolated between the tested doses), and from the non-conservative bias of tests with inadequate statistical power. This approach is referred to as EDx or ECx (effective dose or concentration; x represents the selected effect level of concern).

An example of the ECx approach is in the recommended procedure for analyzing the results of effluent toxicity testing in the USEPA water program (the low effect concentration is defined as the EC_{25}, that is, the concentration that corresponds to a 25 % decrement in response compared to controls).

Work Product

The TRVs for Aroclors have been revisited in Region 5 for application in Superfund sites in which congener data is not available, and for supplemental use to accompany TEQ-based assessments in sites with congener data. Recently, derivation of Aroclor-based TRVs by taking the geometric means of no or lowest observed adverse effect levels (NOAEL or LOAEL), respectively, from selected studies was challenged for including studies with field-contaminated prey that may be confounded by the effects of co-contaminants. The work products under review are the result of combined analysis of studies that reported the reproductive effects of feeding

commercial PCB products to mink and chicken.

The effluent toxicity testing guidance in the water program (e.g., Klemm, et al. 1994; Chapman, et al. 1995) was modified for deriving PCB TRVs from multiple chicken and mink studies. 1) The results of the various studies were normalized so they could be compared on a common basis (the guidance is written for interpreting the results of a single experiment in contrast to the multiple mink or chicken studies performed by different researchers that are analyzed for the PCB TRVs). The normalization was accomplished by dividing each mean treatment response by the respective mean control response. The resulting relative responses are plotted on semi-log graphs (log dose or concentration vs. relative response). The plots showing interpretable dose-response relationships are used to derive the no- and low-effect TRVs by a linear interpolation between the treatments that bracket the effect level of concern. 2) Interpolation is only performed when the effect level of concern falls within the linear portion of the dose-response plot (to avoid uncertain interpolations). 3) A log-linear interpolation is used since it gives a better fit within the linear portion of the data plots compared to the linear interpolation in the guidance. 4) Data are not adjusted when treatment responses exceed control responses (relative responses > 1), since the recommended procedure applies to the results of single, not multiple studies. 5) The procedure for deriving confidence intervals is not implemented since the only available data from the published mink and chicken studies are the treatment means (the underlying data for the individual replicates were not presented for any of the studies).

An alternate approach would be to fit curves to the data, and use the non-linear regressions to calculate the low-effect levels. This approach was not used because only the treatment and control mean responses are reported in the published literature. The underlying replicate data, which would provide the best basis for curve-fitting and are necessary for calculating confidence intervals, are not available.

An additional modification was made for the mink TRVs only. Three studies have shown dramatic increases in adverse effects following continuous exposure to PCBs over 2 breeding seasons or 2 generations of females compared with exposure in 1 breeding season. These studies used field-contaminated prey, or Clophen-supplemented feed, so the 2-season or 2-generation results cannot directly be used to interpolate 2-season or generation Aroclor TRVs. Instead, the 1-season Aroclor TRVs are multiplied by the mean ratio of the available 2-season or generation TRVs divided by the corresponding 1-season TRVs to derive Aroclor TRVs protective for sustained occupancy of a site by female mink.

Literature Cited

Chapman, G., D. Denton, and J. Lazorchak. 1995. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to West Coast Marine and Estuarine Organisms. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA/600/R-95-136.

Klemm, D., G. Morrison, T. Norberg-King, W. Peltier, and M. Heber. 1994. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms, 2nd ed. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA/600/4-91/003.

Leonards, P., T. de Vries, W. Minnaard, S. Stuijfzand, P. de Voogt, W. Cofino, N. van Straalen and B. van Hattum. 1995. Assessment of experimental data on PCB-induced reproduction inhibition in mink, based on an isomer- and congener-specific approach using 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalency. Environ Toxicol Chem 14: 639-652.

Peer Review Charge

The peer review charge is to evaluate the methodology for deriving Aroclor TRVs. The charge does not include review of the input data (although documentation of the data and the specific sources is included in the materials provided to reviewers), but the methodology for normalization of the data is part of the charge.

Charge Questions

Peer Reviewers should comment on the following:

1) Is the data normalization method (relative response = treatment response / control response) appropriate for combining the results of different toxicity studies into single dose- or exposure-response plots? If not, what would be a more appropriate method? Explain.

2) Is the linear interpolation method appropriate for deriving the dose or dietary concentration corresponding to selected effect levels? If not, what method would be more appropriate for use with mean data (when the underlying replicate data are not available)? Explain.

3) Are the effect levels appropriate (75 % relative response for low effect, 100 % relative response for no effect)? If not, what effect levels would be more appropriate. Explain.

4) Are the following modifications of the linear interpolation method recommended for effluent toxicity testing in the Water Program appropriate? If not, how should the method be applied? Explain.

a) Restricting interpolation to the linear portion of the data plots.

b) Use of log-linear interpolation in place of (arithmetic) linear interpolation.

c) No adjustment when treatment response exceed control responses (relative response allowed to exceed a value of 1.0).

d) No confidence interval estimation.

5) Regarding the mink TRVs only, is the procedure for adjusting the TRV based on exposure during a single breeding season to derive a TRV protective for continuous exposure through two breeding seasons or two generations of females appropriate? (The single-season Aroclor TRVs are adjusted by multiplying by the mean ratio of the 2-season or generation TRVs divided by 1-season TRVs from feeding studies with field-contaminated prey or Clophen A50.) If the procedure is not considered appropriate, are there any recommended alternative approaches? Explain.

6) Any other comments on the methodology? [optional]

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5. Consolidated Peer Review Comments and Responses

The peer review questions are shown in bold type. Reviewers are designated by their initials, and the comments are given in alphabetical order of the reviewers' last names. The comments are presented as received, except that internal references to another comment by the same reviewer have been converted to a standard designation (question number and reviewer initials). Responses to specific comments are indented under the particular comment. Individual responses are not made to wholly favorable comments. A summary response for each question is also provided that integrates the individual comments and responses for that question, with the exception of question 6 because the comments do not address a common charge question. Only a summary response is provided if the comments requiring responses can be addressed with a general response.

1) Is the data normalization method (relative response = treatment response / control response) appropriate for combining the results of different toxicity studies into single

dose- or exposure-response plots? If not, what would be a more appropriate method? Explain.

CC: Comparison of similar studies via the data normalization procedure is one of several approaches but yours is probably the best for very small data sets.

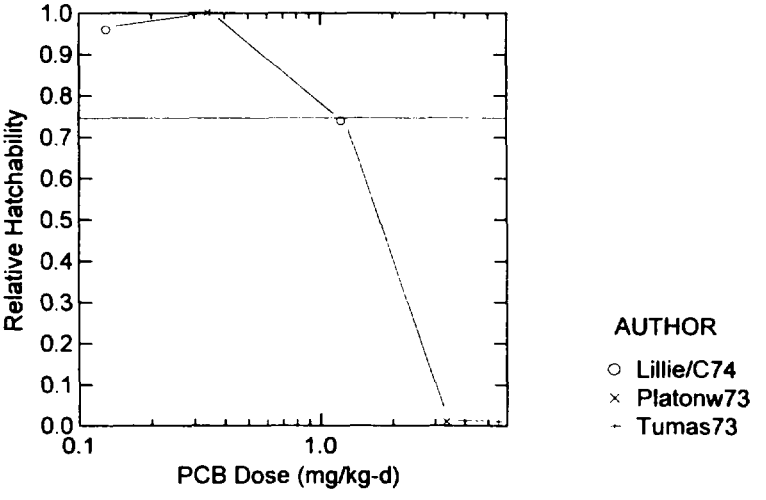
TH: The relative response normalization is appropriate so long as the treatment response and control response are from the same study (i.e., same dosing regimen). As for combining results of different studies, see comment 2 TH.

> Accepted. Normalization is only performed when the treatment response and the control response are from the same study.

DH: This is only appropriate if experimental design portions of the multiple studies are similar. One would NOT want to normalize multiple data sets if one exposure route is of oral exposures by gavage method vs. the other of a contaminated diet. Also, the duration of exposure needs to be similar if not identical. Finally, different strains of organisms can vary in their response. In the example used above with the AWQCs, the organisms used for testing are of known health. This is established as positive control tests are run simultaneously with actual tests using reference toxicants such as KCL. The reference toxicant result (e.g. LC50) must be within a certain percentage of the species mean LC50 for the rest of the test to be valid. Aquatic organisms have always been easier to combine data sets in the way these authors suggest just from the standpoint of assumptions of consistent exposure and duration when an organism is submersed in water are much more robust than when one makes the same assumptions for terrestrial wildlife vertebrate toxicological studies. I believe a much more prudent approach would be develop the dose-response curves (relative response = treatment response / control response; absolutely the way to go) for each study and then use a statistical representation of all the studies (ie, geomean of EC20s).

> Accepted (relative response comment).
>
> Not accepted (study design comments) because examination of the data shows no major impact of these factors on the combined dose-response plots (with the exception of number of breeding seasons or generations exposed for mink, and the effect of A1242 on hatchability–both of which are disaggregated for analysis).
>
> The exposure route for all of the mink studies was the same, that is, through contaminated diet. For oral dose to chicken, the exposure route was contaminated diet with one exception–contaminated water in the study by Tumasonis, et al. (1973). The data do not show an effect related to this difference in exposure media. The relative effect due to exposure to contaminated water is consistent with the effect trends of exposure to contaminated diet (Figures 1 and 3). In any case, because of the high dose in the Tumasonis, et al. study, the results did not directly affect any of the TRV interpolations.

Figure 1. Hatchability vs. A1254 Dose to Hens



For egg concentration, the exposure route was through maternal dietary exposure except for Gould, et al. (1997) in which PCBs were injected into egg yolks. The Gould, et al. study influenced one TRV (chick bodyweight vs. A1242 egg residue). Again, the response trend is consistent between exposure routes (Figure 2).

It was not feasible to exactly match the exposure durations between studies. Exposure duration ranged from 6 to 14 wk for chicken feeding studies (most between 6 and 9 weeks) (a 39-wk treatment by Platanow and Reinhart (1973) was not used for TRV derivation), and from 3 to 10 months for mink studies performed over a single breeding season (the results of the 2-month exposure duration by Jensen (1977) was not used for TRV derivation because the type of PCB used in this study was not identified). For mink, the studies were segregated by the number of breeding seasons exposure was maintained (the results of 2-season or 2-generation exposures are analyzed separately from 1-season results). Again, the data are consistent within the range of exposure durations of the combined studies. For example, the results of three studies were combined to evaluate the effect of A1254 on hatchability. The exposure durations of these studies were 6 wk (Tumasonis, et al. 1973), 9 wk (Lillie, et al. 1974 and Cecil, et al. 1974), and 14 wk (Platanow and Reinhart 1973); however, the relative response plots show internally consistent responses (no obvious duration effects) on the basis of either maternal dose (Figure 1) or egg concentration (Figure 3).

Figure 2. Chick Bodyweight vs A1242 Egg Residue

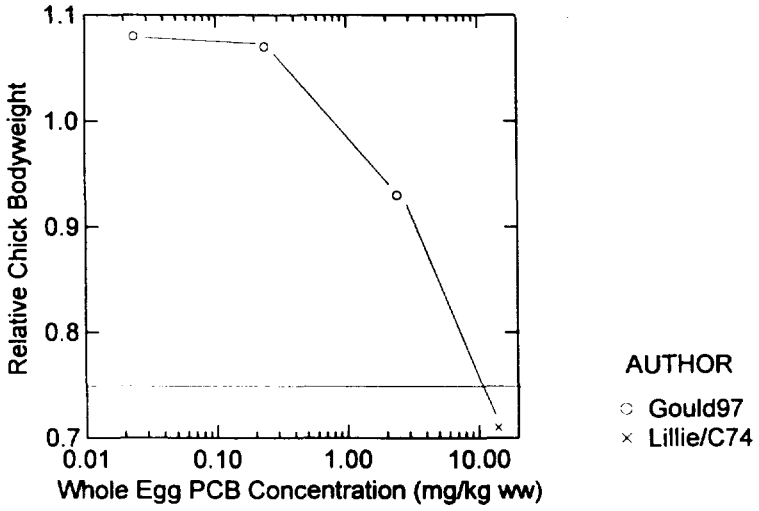
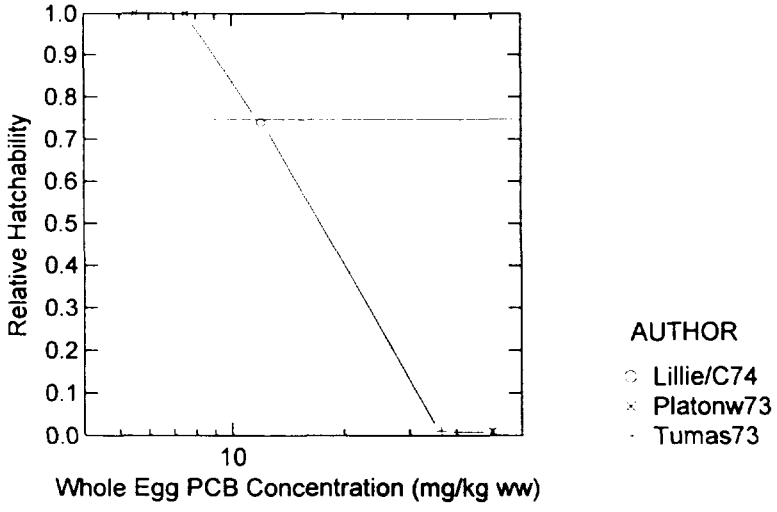
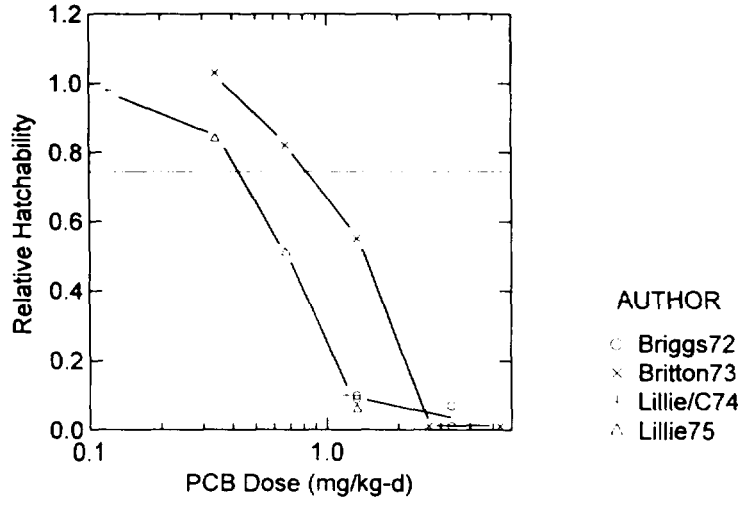


Figure 3. Hatchability vs A1254 Egg Residue



Besides the pronounced difference in the responses of mink to exposures over 1 vs. 2 breeding seasons or generations, the only other endpoint for which exposure duration might have had an influence is the effect of A1242 oral dose on hatchability. Two response trends are evident, one largely driven by 8 to 9 wk exposures (Lillie, et al. 1974, Cecil, et al. 1974, Lillie, et al. 1975), the other by 6 wk exposure (Britton and Huston 1973) (Figure 4). However, the results of the 6-wk exposure study by Briggs and Harris (1972) are consistent with the former trend (8-9 wk exposures), which indicates that the cause of the two response trends for A1242 and hatchability is not related to differences in exposure duration among the combined studies (the doubled data points for Briggs and Harris are because they tested two different chicken breeds). In any case, the divergent results are obvious from the data plot, and are therefore considered separately. There was no obvious exposure duration effect in the other plots.

Figure 4. Hatchability vs. A1242 Dose to Hens

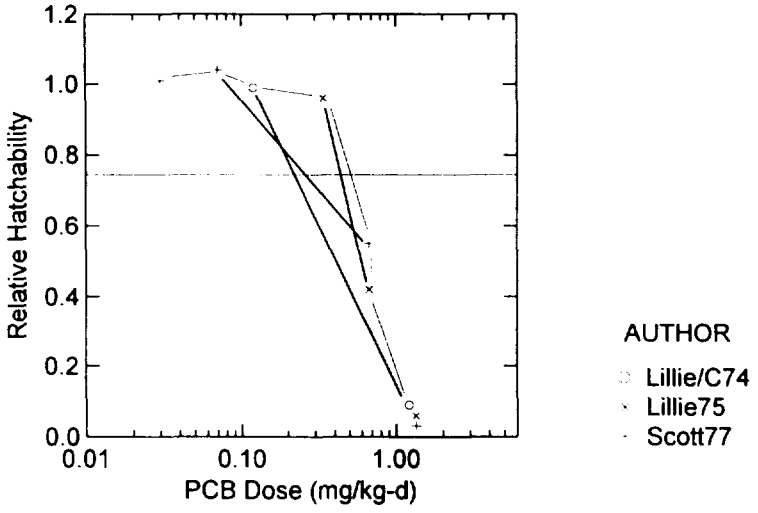


There is no method for retrospectively comparing the possible differences in sensitivity between the strains used in the various studies. However, by restricting TRV derivation to only those endpoints exhibiting reasonably consistent dose-response plots for combined studies, any large effects due to differences in strain sensitivity or health between studies would have disqualified that endpoint for TRV consideration.

Not accepted (geomean comment). The suggestion to derive effect levels individually from separate dose-response curves developed for each study, and then take a geometric mean of the study-specific results, would be appropriate if most of the studies reported

results for a sufficient number and range of concentrations to generate comparable curves. However, the database is too sparse for the suggested approach. For example, there is an internally consistent dose-response plot for the effect of A1248 on hatchability (Figure 5). The 9 mean data points in this plot come from 3 studies–one contributing 4 means, one 3 means, and another 2 means. The ED_{25} for the separate studies are approximately 0.45, 0.25, and 0.2 mg/kg-d, for a geometric mean of 0.3 mg/kg-d (the linear interpolation lines are individually shown for each study in Figure 5). This is more conservative than the ED_{25} of 0.48 mg/kg-d based on the combined data plot, but is less reliable because the shape of the dose-response curve is poorly revealed by 2 of the studies taken individually. In other words, there is greater uncertainty in interpolating TRVs from the dose-response plots of individual studies with low numbers of treatment doses than there is for combined plots. Uncertainty is reduced in the combined plots because the increased number of treatment dose levels better defines the shape of the dose-response relationship.

Figure 5. Hatchability vs. A1248 Dose to Hens



MS: I do not believe that there is any reason for concluding that the normalization approach used is invalid. The only criticism which may be valid is that with limited data sets the normalization may skew the results, however, that interpretation is relative to alternate data evaluations and does not inherently mean it is incorrect.

GS: Yes, the normalization to controls is appropriate.

1) Summary Response

The normalization procedure is acceptable to all the reviewers. While two reviewer raised several questions on combining studies together in dose-response plots, the consistency of the combined data plots indicate that these issues do not have significant effects on the outcomes for the endpoints used for TRV derivation. The sole possible exceptions are the effect of A1242 on hatchability (although other explanations, such as differences in Aroclor batches or experimental conditions, are more likely than differences in exposure duration), and the effect on mink of exposure over 1 breeding season versus 2 breeding seasons or generations. The data are analyzed separately for both of these situations.

2) Is the linear interpolation method appropriate for deriving the dose or dietary concentration corresponding to selected effect levels? If not, what method would be more appropriate for use with mean data (when the underlying replicate data are not available)? Explain.

CC: No relevant comments.

TH: The combining of data from different studies is only appropriate if the data are "the same" with regard to exposure dose metrics (i.e., for this method to be valid apples can only be combined with apples, not with oranges). For example, dosing or exposure regimens (i.e., route and time) must be similar or identical among all studies to be included (only way to exclude response differences that are due to pharmacokinetic factors). This need for consistency in dose metrics is why the reason behind development of *standard* toxicity testing protocols used in conjunction with the WET methodology.

This lack of consistency in dosing regimens is why this type of approach is typically not applied to mammalian/bird wildlife toxicity data or laboratory rodent toxicity data. For example, IRIS toxicity values are generally based on a selected "best" study and adjusted using weight of evidence from other studies because, at least in part, it is inappropriate to combine data due to inconsistencies in dosing regimens. It is worth noting here that during development of the GLWQI wildlife criteria, U.S. EPA (via contractor) explored the possibility of constructing dose-response curves and interpolate EDx values to derive benchmark doses from existing mammalian and bird wildlife Hg and PCB toxicity data. PCB toxicity studies were assembled and reviewed. The pilot PCB analysis used individual dose-response studies (Platonow & Reinhard 1973 data for bird and Bleavins, Aulerich & Ringer, 1980 for mink) presumably for reasons discussed above regarding combining data and included confidence intervals. This cursory analysis did not result in a better estimate of a concern level than the use of the LOAEL determined in the studies. The large confidence interval at the lower doses resulted in interpolated BMD values that were similar to the LOAELs, but with greater uncertainty. It was concluded that to effectively utilize dose-response data and interpolation approaches, it would be necessary to produce appropriate dose-response data for the endpoint(s) of concern. From a quick look at the studies examined for

your effort, there have not been new studies suitable for this analysis (most of the same studies were examined in both efforts.)

> Not accepted for the reasons discussed in the response to 1 DH, and because the example given of the GLI pilot analysis does not include combining data sets from multiple studies to better reveal the shape of the dose-response relationship.
>
> The precision of exposure-response plots is generally improved more by increasing the number of dose levels tested as compared to increasing the number of replicates for the same doses (Crump, et al. 1995). The appropriate comparison would be to contrast the conventional LOAELs from individual studies with the EDx derived from the exposure-response curve based on the combined data of all the relevant studies. Based on the comment, this was not done as part of the GLI pilot analysis. The pilot analysis appears to indicate that TRV derivation may be problematic for single studies with low numbers of dose levels regardless of the particular approach. However, that comparison is not relevant for the approach taken here of combining study results into aggregated dose-response plots.

DH: I would generally support the authors proposed use of the interpolation method. However, I have significant misgivings about NOT being able to include confidence bounds. Have the authors of this document attempted to reach the primary authors of the literature. Many times the raw data can be obtained from the original authors to help finish the analysis. Without including the confidence bounds on the dose-response curves, many of the same appropriate arguments presented in this paper which object to the use of NOAELS and LOAELS will apply in the interpolation method as well. For example, if the confidence limits are large, a NOAEL could be more useful than an EC20 that ranges across multiple doses in the experimental design.

> Accepted (interpolation comment).
>
> Not accepted (raw data comment). This work could be refined by accessing the original replicate data for the studies, which would provide the best basis for curve-fitting and confidence interval estimation, but the effort (for more than 20 studies published over a 30-year period) is not expected to substantially alter the final results. The main reason is because most of the endpoints exhibit very steep dose-response relationships. The relatively small gradient between mean no-effect levels and mean total-effect levels (see 3 Summary Response) constrains the possible values for the TRVs to a narrow range.

MS: I do not see any technically valid reasons for discounting the approach used.

GS: Linear interpolation is an acceptable method. However, I would not rule out the fitting of a function just because the data for replicates are not available. They are not available for calculating the variance on the interpolated estimates either. While you can not estimate the inter-replicate variance, that may not be the most important concern. I would say that in this

analysis you are more concerned about the inter-study variance, which you could capture in the confidence intervals on fitted functions.

Not accepted (interstudy variance comment). While the inter-study variance might exceed the inter-replicate variance, there does not seem to be firm grounds for assuming this *a priori*. It is not clear how a partial estimate of variance would inform decision-making.

2) Summary Response

The majority of reviewers supported the use of the linear interpolation method for interpolating TRVs. One reviewer questioned whether the treatment protocols of the different studies are sufficiently consistent to allow meaningful aggregation of study results into combined plots (a concern shared by another reviewer for Question 1). As discussed in the response to Question 1, the dose-response plots for the endpoints relied on for TRV derivation are internally consistent and do not exhibit significant discrepancies related to differences in exposure metrics (other than exposure to mink over 1 season vs. 2 seasons or 2 generations, which are separately analyzed). Two reviewers questioned the utility of the approach if the raw data were obtained for confidence interval estimation under an expectation that the confidence intervals would be excessively large. The one example given of a pilot effort for the GLI does not directly bear on this question since it apparently did not involve combining data from different studies, and therefore did not assess the potential for better defining the shape of the dose-response relationship that is the main benefit of combining studies. One reviewer recommended estimating inter-study variance even though it would provide a partial estimate of variance.

3) Are the effect levels appropriate (75 % relative response for low effect, 100 % relative response for no effect)? If not, what effect levels would be more appropriate. Explain.

CC: I have seen those effect levels used in other ecological risk assessment without causing a firestorm of protest. Relatively gross effects are often required to cause an observable effect in field populations. A 75 % effect level seems reasonable.

TH: This cannot be judged with the information provided. The value chosen appears to be arbitrary. No scientific rationale or justification is given for selecting the 25 % effect level. Selection of the 25 % adverse effect level based on the WET program guidance is clearly not applicable here because the WET guidance is designed to support compliance with AWQCs, which are derived to protect aquatic COMMUNITIES. Information should be provided that indicates whether 25 % pup or embryo mortality would be expected to adversely affect the populations of mink or bird(s) associated with the site.

Accepted (rationale/justification comment).

Not accepted (pup/embryo mortality comment) (see 3 Summary Response).

DH: How was the 25 % relative response determined to be the critical threshold for the WET program? Was this a science-based or risk-based decision, or one of a question of statistical rigor? The WET program tests principally fat head minnows and ceriodaphnia dubia. Essentially, 3 of 10 individuals from several replicates have to die before a violation under a permit would be issued to the waste treatment operator. I see absolutely no direct correlation with between the testing procedures in the WET protocols and what the authors propose here. The ecologically relevent percent response would be specific to the organism and the endpoint being tested. In other words, I would view 25 % pup mortality in mink much more influential on sustaining a population of mink, compared to the influence on an entire aquatic community existing in waters that presented a 25 % *in vitro* ceriodaphnia mortality (ceriodaphnia always being one of the more sensitive species in the community).

Accepted (see 3 Summary Response)

MS: I defer to others on this issue. I see nothing technically incorrect and personally believe that the approach used has benefits, as being statistically significant does not inherently mean it is important. I can see this approach being criticized as being a means to increase a TRV (or be less protective), however I do not see this as being inherently true.

GS: Acceptability of a level of effect is a policy judgement, but the basis for the choice of 75 % is not stated. If the basis is consistency with past Agency practices, then the level chosen for the low effect level is reasonable. That is, LOAELs established by hypothesis testing are often equivalent to approximately a 25 % decrement in performance. At the other end, no decrement in response is certainly equivalent to no effect.

Accepted (see 3 Summary Response).

3) Summary Response

The majority of reviewers felt that 75 % relative response is an acceptable estimate for the low effect level. One reviewer speculated that it might be insufficiently protective for mink.

The majority of reviewers requested that further explanation be provided for the low effect level choice. The effect levels are not based on receptor-specific life history/population models. The avian TRVs, derived from chicken data, are intended to provide conservative TRVs for application to species of unknown sensitivity to PCBs, for which no single population model would be applicable. The mink TRVs are similarly intended for mammalian receptors of unknown sensitivity to PCBs (this requires bodyweight normalization of the TRVs), in addition to mink for which it is derived. The effect levels used in this effort are chosen for pragmatic reasons–to minimize model

dependence, approximate the power of well-designed toxicity studies, and maintain general consistency in approach with other regulatory uses of toxicity test data. In short, to select a low effect level that is expected to be detectable in a well-designed study, and is reasonably consistent with prior Agency practice. The very steep PCB dose-response plots make the question of the appropriate low effect level somewhat moot, since there is a small range of concentrations between no-effect and total-effects levels. These issues are discussed in more detail below.

A pragmatic consideration is to avoid choosing an effect level for which interpolation may be strongly model dependent. In an examination of aquatic toxicity data sets, Moore and Caux (1997) concluded that interpolation of effect levels becomes strongly model-dependent for less than 10 % decreases in response compared to that of controls (equivalent to >90 % relative response) (see also Scholze, et al. 2001). The various models gave similar results for effect levels based on response differences of more than 10 % compared to controls. A related consideration is the effect level commonly associated with statistically-determined lowest observed effect concentrations (LOECs) in well-designed toxicity studies. The LOECs of the toxicity studies for the AWQC and pesticide programs generally correspond to 20 to 25 % effect levels (75 to 80 % relative response) (Suter, et al. 2000), and interpolation of the 25 % effect level is recommended for effluent toxicity testing (75 % relative response) (e.g., Klemm, et al. 1994; Chapman, et al. 1995). Another pragmatic consideration is consistency with the basis for regulatory decision-making in other programs that utilize toxicity testing results. A *de minimis* effect-level of 20 % (80 % relative response) was identified in one such review (summarized in Suter, et al. 2000) [note: this is not a standard written in the regulations, but the minimum effect level associated with regulatory actions in practice].

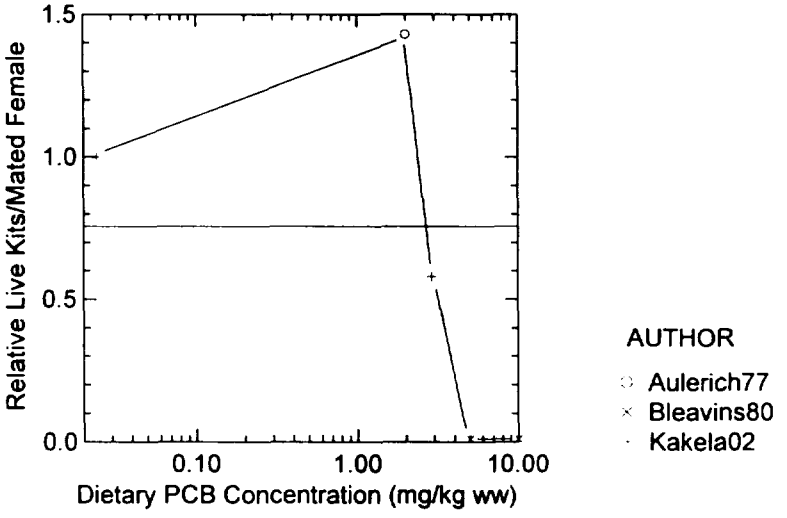
This indicates that a reasonably detectable effect consistent with Agency practices in other programs would fall between 75 and 80 % relative response. The lower end of this range is chosen for this effort to ensure that the low effect level represents a non-trivial departure from the control response. The low effect level could be further refined by linking it to receptor-specific population models to derive effects levels from projected population dynamics (the models probably need to be both region- and habitat-specific). However, because of the nature of the dose-response relationships for PCBs and reproductive endpoints in mammals and birds, such refinement would have relatively minor impact on the final TRV values.

The question of the appropriate value for the low effect level is made somewhat moot by the very steep dose-response plots for PCBs. For example, the A1248 oral dose to hens associated with complete hatch failure (~1 mg/kg-d) is less than 3 times greater than the dose showing no effect (~0.4 mg/kg-d) (Figure 5). The same is true for mink endpoints. Live kit production is completely suppressed at a dietary concentration of 5 mg/kg A1242, but no effect is reported at 2 mg/kg (exposure over a single breeding season) (Figure 6). The range in A1254 dietary concentrations for the same endpoints are 2 and

approximately 1 mg/kg, respectively (Figure 8). Refinements of the effect level will therefore produce only relatively small changes in the derived TRVs.

Although not criticized by the reviewers, the effect size for the no effect TRV will be changed to 10 % (90 % relative response) so that both TRVs will be derived through the same procedure at effect sizes that are not strongly model dependent.

Figure 6. Live Kits per Mated Female Mink vs. Dietary A1242 Concentration, Exposed One Breeding Season



4) Are the following modifications of the linear interpolation method recommended for effluent toxicity testing in the Water Program appropriate? If not, how should the method be applied? Explain.

4a) Restricting interpolation to the linear portion of the data plots.

CC: Given the limitations of using a single study to derive a TRV, it would seem to be sound policy to interpret the data conservatively. Limiting the interpolation to the linear portion is a reasonable approach.

Clarification: the majority of the TRVs are not interpolated from single studies.

TH: OK. This is a statistical approach issue, not specific to WET methods.

DH: No response.

MS: I believe the answer to these questions is simply that I do not see anything which is incorrect or violates some assumption; however I would defer to others on this issue.

GS: It is not clear how this restriction was applied. Looking at the plots, the transition from nonlinear to linear segments is unclear. This is a matter of judgement, but I would be inclined to drop this restriction. I do not believe that nonlinearity between dose levels is a significant source of error relative to other assumptions involved in TRV derivation.

> Accepted (clarification of restriction). The restriction is better described as restricting TRV interpolation to the steep portion of the dose-response plots (visually determined). There are two purposes: 1) the linear interpolation method is applicable to linear responses, but will over- or underestimate for nonlinear portions of the dose-response relationship; and 2) this avoids interpolation over excessively large exposure gradients for which the shape of the dose-response relationship is poorly known. The practical result is that most of the interpolations are performed between relatively small gradients in exposure values. The majority of the TRV interpolations for mink occur between treatments that differ in dietary concentrations by 3-fold or less, with the largest difference (5-fold) for the interpolation for Clophen A50 and live kits. Interpolation is not performed for the TRV for A1254 and kit survival, for example, because there is a 100-fold difference between the dietary concentrations of the treatments that bracket the target low-effect response. Many of the chicken TRVs are interpolated between small gradients in dose (2-fold or less for A1242 or A1248 and hatchability, and less than 4-fold for A1254 and hatchability) or egg residues (2-fold or less for A1242 or A1254 and hatchability, 6-fold for A1242 and chick bodyweight, and 7-fold for A1248 and hatchability). Some of the chicken TRVs are interpolated within 10-fold differences in treatment exposures (A1242 or A1248 dose and chick bodyweight, A1248 dose and survival, and A1242 egg residue and chick bodyweight). Confidence in the interpolations made within 10-fold exposure gradients is less than for interpolations made within smaller gradients. Discussion of this issue will be added to the report.

4a) Summary Response

> The majority of reviewers felt that restricting interpolation to the linear portion of the dose-response plots is acceptable. One reviewer suggested it might be overly cautious, and commented that the basis for applying this criteria is not clear. The linear portion of the dose-response plots is visually determined. Due to the shape of the PCB dose-response relationship (steep slope between no effect and total effects), the restriction resulted in not allowing interpolation when the exposure gradient for interpolation was greater than 10-fold.

4b) Use of log-linear interpolation in place of (arithmetic) linear interpolation.

CC: No relevant comments.

TH: OK. This is a statistical approach issue, not specific to WET methods.

DH: This is probably the best. See additional recent guidance RAGS 3 and chapter 4 of the probalistic guidance to help choose best models. There is actually a mink example.

MS: I believe the answer to these questions is simply that I do not see anything which is incorrect or violates some assumption; however I would defer to others on this issue.

GS: Distributions of toxic responses are typically more similar to log normal than normal distributions. Therefore, the log-linear interpolation is appropriate.

4b) Summary Response

> The majority of reviewer approved of log-linear interpolation, and no objections were raised.

4c) No adjustment when treatment response exceed control responses (relative response allowed to exceed a value of 1.0).

CC: When treatment response is greater than the control response, two things come to mind. Either small doses of PCBs confer some survival advantage to the offspring **or** that the data are so variable that you can't tell one point from another. I would attempt to determine possible explanations for the effect before dismissing (not adjusting) the low dose effect. If highly variable results can't otherwise be explained, I would hesitate to use them. (See further comments below).

> Accepted (see 4c Summary Response)

TH: In performing dose-response modeling, the shape/slope of the curve is obviously determined by the data, both the associated concentration and response ranges. Care should be taken not to "overweight" the dose-response curve with no effect data, i.e. too many zero responses (RR $\geq$ 1) can affect ECx values.

> Accepted. However, the caution regarding the potential bias of oversampling within the no-effect range applies to the influence of an unbalanced sample design on regression performed over the full data range. The linear interpolation method implemented here is not affected by the number of no-effect doses included in the combined data base (so long as the overall dose-response plot show an interpretable relationship), since interpolation is performed only between the treatments that bracket the target response.

DH: No response.

MS: I believe the answer to these questions is simply that I do not see anything which is incorrect or violates some assumption; however I would defer to others on this issue.

GS: This issue depends on whether it is believed that the greater-than-control responses are due to random variance or due to a hormetic effect. The smoothing recommended by Klemm et al. is consistent with the former. The interpolation is consistent with the latter. I recommend that the author review the PCB literature for evidence of hormesis. That is, is improved performance typical of low exposure levels in vertebrates? If so, the interpolation is correct. If not, smooth the data.

Accepted (see 4c Summary Response)

4c) Summary Response

The majority of reviewers recommended further consideration of responses that exceed the control response to determine whether the exceedance is potentially due to hormetic effects (enhanced performance at low exposure levels) or random fluctuations around the control mean. One of the response patterns used for avian TRV derivation, chick bodyweight vs. A1242 egg residues (Figure 2), was attributed to hormesis by the investigators (Gould, et al. 97). The same investigators also reported a hormetic effect of A1254 on chick bodyweight (not used for TRV derivation because the relative response of the highest dose treatment exceeded the low effect target of 75 %). Gould, et al.'s conclusion is accepted because hormesis is evident at 2 dose levels and for 2 different endpoints. There are indications of a possible hormetic effect on hatchability for both hen dose and egg residues, but the effect is minor, at best, for this endpoint, is not readily distinguishable from fluctuation around the control mean, and, in any case, has no significant influence on the TRVs. In contrast, all three of the commercial PCB products tested in mink feeding studies show possible hormetic effects on the number of live kits per mated female (Aroclors 1242 and 1254, and Clophen A50) (Figures 6-8). Hormesis is evident in the Clophen A50 experiment for exposure durations of both 1 and 2 breeding seasons (Figure 7). This effect is also shown by some of the feeding trials performed with field-contaminated prey. In addition, some field-contaminated feeding studies and the Clophen A50 study show possible hormetic effects for kit bodyweight not evident in the Aroclor studies, but the dose levels for the latter may be spaced such that a hormetic effect is not revealed.

In summary, acceptance of potentially hormetic responses is justified for the effects of egg residues on chick bodyweight (as attributed by the researchers), and the effect of dietary exposure on the number of live kits per mated female (exhibited in multiple studies). This indicates that adjustment of deviations in monotonicity is unwarranted. The same modification to the linear interpolation method to allow for potential hormesis was made in a recent comparison of techniques for calculating effect levels (Isnard, et al. 2001).

Figure 7. Live Kits per Mated Female vs. Dietary Clophen A50 Concentration, Exposed One or Two Breeding Seasons

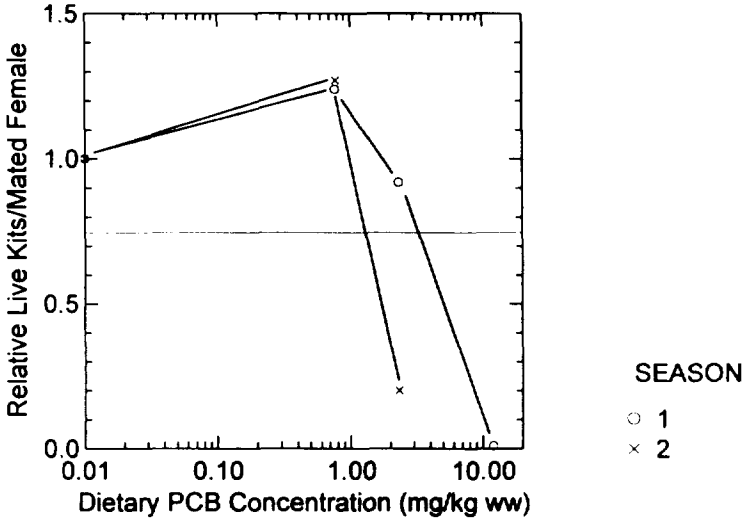
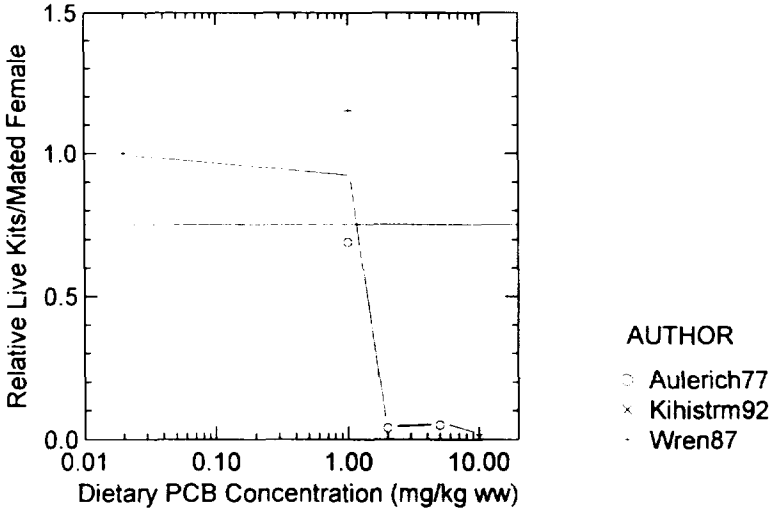


Figure 8. Live Kits per Mated Female vs. Dietary A1254 Concentration, Exposed One Breeding Season



4d) No confidence interval estimation.

CC: Lack of CIs is one consequence of using a single study and no access to original data.

Clarification: the majority of the TRVs are not interpolated from single studies.

TH: NO. This is a major shortcoming of this approach. Not having any sort of confidence interval prevents any sort of assessment as to whether this approach is any better than the NOAEL/LOAEL approach and/or best professional judgement. If no "benefit" (i.e. less variability; less uncertainty, etc.) of this approach can be demonstrated why go through all these mathematical gyrations?

Original data are often available from study authors. Where study authors contacted for data? If not, acquiring the data would go far in improving this effort (i.e., confidence intervals may be calculated, see part d below).

Not accepted. Confidence intervals are not the only procedure for comparing alternative approaches, and, in any case, confidence intervals can not be calculated for either the NOAEL/LOAEL approach or professional judgement (although confidence intervals could be estimated for the latter, it would be an informed guess, not a calculable quantity). Since neither uncertainty or variability can be quantified for NOAEL/LOAEL or professional judgement, it is unclear how the uncertainty or variability of the EDx approach can be compared to the other approaches mentioned in the comment.

An alternate procedure for comparing the results of different TRV approaches is to examine where the TRVs fall on the dose-response plots. For example, consider the exposure-response plot for Clophen A50 and the number of live kits per mated female mink (Figure 7). The data come from two studies (Brunström, et al. 2001; Kihlström, et al. 1992). The LOAEC for this endpoint for exposure over a single breeding season is 12 mg/kg for Kihlström, et al. (1992) and none of the treatments in Brunström, et al. (2001). The Kihlström, et al. LOAEC resulted in 100 % kit mortality–an excessively large effect to be validly considered the lowest dietary concentration associated with adverse effects, however, Kihlström, et al. did not have a treatment with a lower concentration (besides the control). The Brunström, et al. single-season exposure NOAEC is 2 mg/kg. The interpolated low-effect TRV is 3 mg/kg. Similarly, the 2-season exposure LOAEC for Brunström, et al. is 2 mg/kg, but it resulted in an 80 % decrease in live kits per mated female–again, an excessively large effect. The 2-season exposure NOAEC is 0.08 mg/kg (Brunström, et al. 2001). The interpolated low-effect TRV is 1.3 mg/kg. In both of these examples, the statistically derived LOAECs are too high (result in excessively large adverse effects) because of the limitations of the study designs.

DH: No, see comment above (2 DH).

Not accepted (see response to 2 DH).

MS: Relative to confidence intervals, I am not sure that there is even an option, given the limited data sets available.

GS: The bootstrap method to calculate confidence intervals on interpolations presented by Klemm et al. is not applicable to this data set, since the data for responses of replicates are not available. I do not know of any other method that would be applicable.

4d) Summary Response

The majority of reviewers agreed that confidence interval estimation is not feasible when the replicate data are unavailable. Two reviewers considered this a major shortcoming of the approach, and recommended obtaining the original data (see 2 DH and response).

5) Regarding the mink TRVs only, is the procedure for adjusting the TRV based on exposure during a single breeding season to derive a TRV protective for continuous exposure through two breeding seasons or two generations of females appropriate? (The single-season Aroclor TRVs are adjusted by multiplying by the mean ratio of the 2-season or generation TRVs divided by 1-season TRVs from feeding studies with field-contaminated prey or Clophen A50.) If the procedure is not considered appropriate, are there any recommended alternative approaches? Explain.

CC: Given your limited data set, I really like how you dealt with the issue of the greater toxicity following longer exposure. I haven't seen it done before but is seems reasonable and does fit the observed data.

TH: I do not think this approach, as presented, is appropriate. Scientifically defensible rationale for making this adjustment are not provided. What are the reasons (i.e. toxicological mechanisms) that the 2-season/field-contaminated studies yielded more toxicity? The approach used implies it is simply time (i.e., cumulative dose is greater in the two season study, hence the adjustment is essentially a sub-chronic to chronic adjustment), but it is not clear that this is the primary reason for the difference. A plausible reason for the increased adverse effects in the second year studies is the presence of other contaminants in the field-contaminated prey. At least two of the two season studies are confounded by the presence of contaminants other than PCBs, which is the same reason used elsewhere to exclude data for derivation of the TRV. Hence there appears to be arbitrary application of the "co-contaminant" criteria.

Not accepted. One of the studies that continued exposure through more than one breeding season was performed with a commercial PCB (Clophen A50) added to the mink diet by the investigators (Brunström, et al. 2001). This study showed a dramatic decrease in the whelping frequency from 90 % of mated females for the first breeding season to 39 % for the second season in the "A50 high" treatment (2.3 mg/kg diet). The

control whelping frequency was 93 % in both years. Live litter size per whelping female decreased nearly by half between the two exposure periods for the same treatment (from 3.8 live kits/whelped female the first year to 2.0 the second year) (control values 4.0 and 4.4, respectively). Mean kit bodyweight also decreased for this treatment (from 7.9 g to 6.7 g) (control values 9.6 and 8.9, respectively). Only kit bodyweight was statistically discernible from control in the first breeding season, but, in addition to kit bodyweight, both whelping frequency and live litter size per whelped female were also statistically discernible from control values in the second breeding season. In contrast, none of these responses were discernible from the control in the "A50 low" treatment (0.8 mg/kg dietary concentration) in either exposure period (maximum control dietary concentration was 0.01 mg/kg total PCB). The increased severity of 2-season exposure in this study cannot plausibly be attributed to non-PCB contaminants (with the possible exception of co-contaminants formed during the production of commercial PCBs, to which receptors are necessarily exposed as part of their exposure to PCB waste material, and therefore form an integral component of the toxicology of PCB wastes). The investigators speculated that the increased toxicity in the second breeding season may be related to increases in mink PCB body burdens, and emphasized the importance of long-term exposure periods for determining the toxicity of PCBs to mink:

> "In the second season, the effects on reproduction were more pronounced and clearly dose dependent... In our study, the concentration in the feed was the same during the two reproduction seasons, resulting in a reduced frequency of whelping females in the second season only. This finding suggests that the PCB concentration in the animals increased from the first to the second reproduction season, showing the relevance of long-term exposure for estimation of a LOAEL." (Brunström, et al. 2001).

In terms of the endpoint assessed in this effort, the mean number of live kits per mated female decreased from 92 % of the control value at 2.3 ppm PCB dietary concentration for exposure over 1 breeding season, to only 20 % of the control value at the same dietary concentration for exposure over 2 breeding seasons (Figure 7). Accordingly, the interpolated low-effect level for 2-season exposure is less than one-half of the 1-season low-effect level.

The difference in severity between 1-season exposure versus 2-season or 2-generation exposure in the study using field-contaminated prey by Restum, et al. (1998) for number of live kits per mated female (2-season is less than 40 % and 2-generation is less than 30 % of the 1-season low-effect level) are close to the difference in the same endpoint for the Brunström, et al. (2001) study using a commercial PCB product (2-season is 40 % of the 1-season low-effect level). This indicates that the effect is likely attributable to PCB exposure and is not an artifact of some non-PCB co-contaminant unique to the study using field-contaminated prey. In addition, the field-contaminated prey used in the Restum, et al. (1998) feeding study were collected at one time, homogenized, and stored for use throughout the study, so the increased severity of the effects for 2-season or 2-generation exposure cannot be attributed to changes in co-contaminant levels between the

first and second exposure periods.

The duration effect is observed for multiple endpoints–in addition to number of live kits, two other endpoints (kit bodyweight and survival) reported by Restum, et al. (1998) also show increased severity with exposure over 2 breeding seasons (70-90 % of 1-season low-effect level) or 2 generations (40-60 % of 1-season low-effect level). Kit bodyweight also was more affected by 2-season exposure compared to 1-season exposure in the Clophen A50 study (unfortunately, kit survival was reported for 2-season exposure, but not for 1-season) (Brunström, et al. 2001). The Restum, et al. (1998) study also shows that the exposure duration effect can occur through two different exposure scenarios–either breeding females continuously exposed over 2 breeding seasons, or females first exposed *in utero* with exposure continued through their first breeding season (combined fetal and adult exposure over 2 years).

To summarize, there are multiple lines of evidence that continued exposure to PCBs through more than one breeding season increases the severity of the adverse effects in mink compared to single-season exposures. The exposure duration effect has been observed by different research groups using different contaminant sources, and for multiple endpoints through different exposure scenarios, so it is unlikely that the duration effect is the result of chance fluctuations in the results of any particular experiment. In order to be protective of sustained occupancy of contaminated areas by mink, the increased severity of prolonged exposure should be taken into account.

While it would be useful to understand the biochemical and physiological processes responsible for the observed exposure duration effect, this is not a prerequisite for assessing risk or informing risk management decisions. For example, while the toxic effects of dioxin-like chemicals are known to be mediated through the aryl hydrocarbon receptor (AhR) which results in activation of certain genes, there are significant gaps in our understanding of the underlying processes. For example, the physiological role of AhR is only partly known (Puga, et al. 2002; Hahn 2002), the array of genes modulated by AhR has not been fully identified (Lai, et al. 1996), and there is a "true lack of knowledge of the exact biochemical pathways which are altered by PHHs [planar halogenated hydrocarbons] and subsequently lead to the adverse effects on whole organisms" (Tillitt 1999). However, the lack of a complete physiological explanation for AhR-mediated effects does not prevent assessment or regulation of risks to dioxin-like compounds because AhR induction has been empirically correlated with toxic responses to dioxin-like chemicals.

To address another issue raised in the comment, there is no arbitrary application of the "co-contaminant criteria". Studies using field-contaminated prey are not directly used for deriving effect levels since the particular effect levels may be influenced by contaminants other than PCBs. One study using field-contaminated prey was used, along with a commercial PCB feeding study, to estimate the ratio of the 1-season versus 2-season or

generation effects. As discussed above, the exposure duration effect observed in the Restum, et al. (1998) study cannot be attributed solely to co-contaminants since the same effect occurred in a commercial PCB feeding study, and cannot be attributed to changes in co-contaminant concentrations between the years the study was run because all of the field-contaminated prey were collected at one time, homogenized, and stored for use throughout the experiment. The sole use of the Restum, et al. (1998) study in the present effort is to help estimate the proportional change in mink endpoints when the exposure duration is increased from 1 breeding season to 2 breeding seasons or generations, so that the 1-season Aroclor TRVs could be adjusted to account for the increased toxicity observed in other studies for exposures of longer duration. As such, it lends support to the exposure duration effect shown in the commercial Clophen A50 study, and provides evidence that the effect is not unique to European commercial PCBs.

DH: I would say no. Again, the core of the problem would be the comparibility of the field-contaminated prey vs. the laboratory mixture of Aroclors exposed in the 2 generation study. I would generate an average ECx of the two studies after one year and compare that to the same ECx after 2 years. If they are signifcantly different, reduce the corresponding dose of the average ECx after one year to be equal to that of the corresponding dose at the appropriate ECx after 2 years.

Not accepted. See 5 TH for the comparability issue. It is not clear how averaging the results of the study using field-contaminated prey with those of the study with Clophen A50 added to the mink diet would improve (or even assist) analysis of the results, since there is no necessary expectation that the particular dietary concentrations associated with effects would be identical for a European commercial PCB product and the PCBs accumulated by fish from a waterway contaminated by an American PCB product. One of the underlying assumptions of the approach taken in this effort is that the different PCB products do not necessarily exhibit the same degree of toxicity, and therefore require separate analysis.

MS: I believe approach used is valid and a significant improvement in the formal evaluation of the toxicity data. Certainly, time dependent exposure is an important factor in the response of organisms, and long term accumulators, like PCBs, should be evaluated in this manner or a similar one.

GS: Since there seems to be a consistent increase in effects over time, it is appropriate to adjust for it. The simple method used here is reasonable, and I do not believe that the available information could support a more sophisticated method.

5) Summary Response

The majority of reviewers approve of the method used to account for the observed increased severity of the effects in mink for continuous exposure to PCBs over 2 breeding

seasons or over 2 generations of females compared to the effects for exposure over a single season to a single generation. One reviewer suggested that the duration effect may be attributable to co-contaminants (other than PCBs), but the evidence does not support this conjecture. An alternate approach suggested by one reviewer would not improve the analysis.

6) Any other comments on the methodology? [optional]

CC: Being a pragmatist, I appreciate having to come up with solutions to thorny problems with very limited data. Given the few comparable studies that you had to work with, your options are limited. For years, we developed References Doses for human exposure based upon a single, 'best' study (with supporting studies). It worked pretty well but a consequence was the requirement for high Uncertainty Factors and the potential for gross overprotection. Eventually, we developed techniques such as the Benchmark Dose for using the information in multiple studies and the methods to make the studies more comparable. i.e. The information in multiple, somewhat comparable, studies results in less uncertainty and lower UFs. We need to work toward developing methods for combining similar study results to make better use of limited data.

TRVs were derived for specific Aroclors with consideration of preference for chronic exposure studies and multi-generation and multi-year exposures. I have read the discussions on the rationale for not requiring statistical significance as a selection criterion. I also understand some of the limitations introduced by the effect of dose spacing and that the lack of statistical significance does not negate the potential for significant toxicity. But if the variability between treatments is so high that you can't distinguish between them statistically, they should at least show a significant trend. I would be more sanguine if several studies could be combined in a meta-analysis for trend and the significance of the slope.

You make a good case that, for individual Aroclors, there are insufficient studies for a meta-analysis. So be it. But we should be working toward making TRVs based on single studies a thing of the past. Issues such as weathering (see below) argue for a TEQ approach. Either from a mixtures approach or congener analysis. The issue of how the TEFs were derived is not that difficult. For most of the laboratory studies, used in our dioxins dose-response analysis, we converted the doses of specific congeners to TEQs based upon the WHO (van den Berg, et al. 1998) and Agency TEFs (U.S. EPA. 2002) for wildlife.

Not accepted (meta-analysis comment). No claim is put forth that meta-analysis is infeasible. Meta-analysis is an alterative approach to the one implemented here. It probably would be an improvement over the statistical analyses in the original studies in that the statistical power should increase as a result of the increased sample size of the combined studies, but the TRVs would still be subject to the inherent limitations of the statistically-driven NOAEL-LOAEL approach (TRV selection limited to the particular dose levels used in studies, statistical significance affected by factors independent of

toxicity, that is, the various factors that affect the power of the statistical tests employed, and inconsistencies between studies in the severity of the effects for the same TRV, for example, effects to as much as 50 % of the test population have been identified as NOAELs in some studies (Crane and Newman 2000)). The present effort explicitly combines the results of different studies to generate aggregated dose-response plots for TRV derivation, and therefore does not base TRVs on single studies as implied in the comment.

The comment on the TEQ approach is addressed in the next response.

Another issue is the selection of specific Aroclors (rather than total PCBs or specific congeners) upon which to base a TRV. There is a discussion about the relevance of a TRV for Aroclor 1254 following weathering and environmental compartmentalization. The end result could be more or less toxic than the parent PCB mix. Additional complexity is added if other Aroclors are part of the mix. Since PCBs are among the several dioxin-like compounds that exert much of its toxic effect via Ah-receptor binding, TRVs based on the level of Ah-R activity in the relevant media avoid the uncertainties of weathering and complex mixtures.

Another approach, using the toxicological equivalence of Ah-R binding is the Hazard Index Approach for mixtures that act by similar mechanisms. Since the TRV approach involves specific Aroclor analysis, identification of specific PCB congeners would allow addition of their toxicological equivalents and comparison with some reference standard. I recommend you discuss alternatives to your method for deriving the TRV in the text of the document.

Accepted, a discussion of alternative approaches will be added. A point of clarification–the PCB TRVs are not intended to replace congener-specific approaches. The rationale for developing Aroclor-based TRVs, as discussed in the background to the peer review charge, will be incorporated in the TRV memo.

My editorial comments are few. I recommend changing the way you present the no-effect and low-effect TRVs. I suggest the following example (page #1; paragraph #4): "The dietary TRVs for A1242 are 1.3 and 1.4 mg/kg for live kit production (no-effect and low-effect, respectively), adjusted for ....." This confusing notation appears throughout the document.

Accepted. The notation will be changed as suggested.

Finally, it is not clear from your citation (Leonards, et al. 1995)(Table 2) in your discussion of response normalization (page #3; paragraph #1) that you are referring to a methods citation rather than data which might appear in Table 2.

Accepted. The citation is for the method, not the data. The text will be clarified.

CC References

U.S.EPA. 2002. Framework for Application of the Toxicity Equivalence Methodology for Polychlorinated Dioxins, Furans and Biphenyls in Ecological Risk Assessment - External Review Draft. National Center for Environmental Assessment, Risk Assessment Forum. www.epa.gov/ncea/raf

van den Berg; et al. 1998. Toxicity Equivalency Factors (TEFs) for PCBs, PCDDs, PCDFs for Humans and Wildlife. Env.Health Per. Vol.106, No.12, 775-792.

TH: TRVs are derived for several different Aroclors and apparently specific TRVs will be selected for use based on Aroclors detected at a specific site. In implementing such an approach it should be recognized that there are major uncertainties associated with 'defining' Aroclors present at a given site, and that selection of a specific (single) Aroclor TRV for use in the risk assessment perpetuates this uncertainty. Generally, PCBs often cannot be adequately described by reference to Aroclors due to the subjective assignment of congener and response factors. Aside from these analytical uncertainties, there is great uncertainty associated with the assumption that Aroclors are representative of weathered PCB profiles. Together, these factors present major uncertainties associated with the nature and extent of PCB exposure in the risk assessment. To be selective in characterizing effects based on exposure data with such uncertainties may add significant additional uncertainty (i.e., to 'select' a single Aroclor TRV to use in effects characterization, based on very uncertain exposure characterization–single Aroclor). Perhaps it would be prudent to calculate risk estimates using each of the Aroclor TRVs and present a range of potential risk estimates which represent the potential variance in the PCB profiles present.

> Accepted. The uncertainties associated with basing risk estimates on Aroclor data will be discussed.

DH: No response.

MS: Overall, I believe the approach taken is valid and a significant improvement in the formal and objective interpretation of the literature toxicological information.

If the opportunity presents itself for revision of the materials provided it would be useful to present all of the concentrations and exposures in one set of units, currently there is some mixing which creates a little extra mental work for the reader.

> Accepted (in part). The use of "ppm"will be changed to "mg/kg" for consistency with the rest of the report.
>
> Not accepted (in part). The chicken TRVs are unavoidably expressed in two different units: mg PCB/kg_{BW}-d for oral dose to adult hens, and mg PCB/kg egg for egg concentrations. It is not possible to convert these units to a common basis since they represent different measurements. The mink TRVs are given as mg PCB/kg diet. The

mink TRV is expressed in terms of dietary concentration, instead of bodyweight-normalized dose, to simplify the risk calculations at sites for which mink is a selected endpoint. Since the feeding studies were performed with mink, it is not necessary to convert the dietary exposures to bodyweight-normalized doses to characterize the risk to mink. However, for conservatively estimating risk to other mammal species that lack PCB toxicity data, the mink dietary TRVs (mg PCB/kg food) can be generalized for interspecific extrapolation by multiplying by the mink bodyweight-normalized food ingestion rate (kg food/kg_{BW}-d) to obtain the oral dose TRV (mg PCB/kg_{BW}-d).

In future evaluations I suggest that we are open to the inclusion of gray literature in the evaluation of TRVs, I believe that the original gray literature (e.g. thesis or study report) could provide greater insight into the best interpretation of the data generated by the study.

Accepted for future evaluations. For the objectives of the present effort, the exclusion of gray literature does not have a significant effect. No unpublished feeding studies performed with commercial Aroclor are known. Some mink feeding studies with commercial Clophen or field-contaminated fish have not been formally published and are therefore excluded, but none of these would affect the commercial Aroclor-based TRVs developed in this effort.

GS: This is not a criticism, but rather a point to consider. The conventional TRVs have two values because of the peculiarities of hypothesis testing based test endpoints. The NOAEL is nominally a no effect level and the LOAEL is nominally a significant effect level. Hence, the threshold from no effects to potentially significant effects must lie somewhere in between. If you are using a biological effects level, there is no need for a two-valued TRV. You could simply choose an effects level as the threshold.

Not accepted for presentation. Representation of the range between the highest dose associated with no adverse effects and the low-effect dose (such as the ED_{25}) is useful information for risk managers regardless of whether the values are statistically determined (conventional NOAEL-LOAEL) or based on the shape of the dose-response relationship (interpolation). Presenting risk managers with a range of preliminary remedial goals (PRGs) corresponding to the no- and low-effect levels allows the managers greater flexibility in satisfying the 9 criteria for remedy selection as compared to providing only a single PRG. A no-effect PRG is useful because it sets a lower limit to remedial goals below which no incremental reductions in risk to wildlife are expected. Conversely, the low-effect PRG sets an upper limit above which detectable adverse effects may occur. Depending on the slope of the dose-response curve, the gradient between the no- and low-effect values may be large or small, with corresponding implications for the range of remedial options that may be considered by decision-makers.

Accepted for results. When the no effect TRVs are interpolated as ED_{10}, the range

between no effect and low effect TRVs are exceedingly small, such that the result for practical purposes is a single threshold.

The figures are very hard to read when printed. Also, it would be easier for the reader to judge the reasonableness of the TRVs if they were marked on every plot (e.g., with vertical dashed lines). It would also make the methods clearer if you indicated on the figure from which the TRVs were derived, the points between which you interpolated (e.g., by connecting them with a line).

Accepted (in part). The figures are modified by linearly connecting the data, and by marking the 0.75 relative response low-effect target value. The intersection of a linear segment and the 0.75 relative response line represents the interpolated low-effect concentration or dose. The data points used for the interpolation are the two points closest to this intersection, and are given in the interpolation tables. The no effect values are similarly interpolated (in the case of hormetic responses) for 1.0 relative response (not drawn in the figures).

Not accepted (in part). The suggested vertical lines are not inserted because the TRVs are calculated and not derived through a graphical approach. Since graphical and mathematical approaches may differ somewhat, the vertical lines are not inserted to avoid misunderstanding. This will be clarified in the report.

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Original Peer Review Comments
Submitted by Email in Response to
Peer Review Charge for Mink and Chicken PCB Toxicity Reference Values
Derived Through an EDx (effective dose) Procedure

Received 10/17/02 through 11/14/02

Including Responses to Comments and Questions Outside of the Peer Review Charge

10/18/02 and 11/1/02

MEMORANDUM

DATE: October 29, 2002

SUBJECT: Review of Draft Avian PCB Toxicity Reference Value (TRV)

FROM: Chris Cubbison, Ph.D.
Environmental Health Scientist
National Center for Environmental Assessment (NCEA)

TO: James Chapman, Ph.D.
Ecologist
Region 5

Thank you for the opportunity to comment on the draft Avian PCB Toxicity Reference Value (TRV). I have reviewed the TRV and associated methodology and find the approach to be scientifically reasonable. The approach taken in deriving the TRV should be reasonably protective of birds which are highly sensitive to PCB toxicity. Furthermore, the endpoint selected as the basis for the TRV, reproductive and developmental toxicity, is ecologically relevant and occurs at lower concentrations than most other endpoints. Exposure standards based upon the Avian TRV should be protective of most other exposed birds.

TRVs were derived for specific Arochlors with consideration of preference for chronic exposure studies and multi-generation and multi-year exposures. On thing that is unclear (first paragraph of the Methods section) is why statistical significance was not a selection criterion. I understand that many, well conducted, studies lacking statistical significance can be combined in a meta-analysis to demonstrate significant trends. But that is not what was done here. If the variability between treatments is so high that you can't distinguish between them statistically, they should at least show a significant trend.

Another issue is the selection of specific Arochlors (rather than total PCBs or specific congeners) upon which to base a TRV. There is a discussion about the relevance of a TRV for Arochlor 1254 following weathering and environmental compartmentalization. The end result could be more or less toxic than the parent PCB mix. Additional complexity is added if other Arochlors are part of the mix. Since PCBs are among the several dioxin-like compounds that exert much of its toxic effect via Ah-receptor binding, why not base a TRV on the level of Ah-R activity in the relevant media. Another approach, using the toxicological equivalence of Ah-R

binding is the Hazard Index Approach for mixtures that act by similar mechanisms. Since the TRV approach involves specific Arochlor analysis, identification of specific PCB congeners would allow addition of their toxicological equivalents and comparison with some reference standard (U.S.EPA Great Lakes Initiative). I recommend you discuss alternatives to your method for deriving the TRV.

My editorial comments are few. I recommend changing the way you present the no-effect and low-effect TRVs. I suggest the following example (page #1; paragraph #4): "The dietary TRVs for A1242 are 1.3 and 1.4 mg/kg for live kit production (no-effect and low-effect, respectively), adjusted for ....." This confusing notation appears throughout the document.

Finally, it is not clear from your citation (Leonards, et al. 1995)(Table 2) in your discussion of response normalization (page #3; paragraph #1) that you are referring to a methods citation rather than data which might appear in Table 2.

I hope that these comments are helpful and I would be happy provide further information if you have any questions or need additional input. I can be reached at 513 569-7599 or at cubbison.chris@epa.gov.

cc:

MEMORANDUM

DATE: November 14, 2002

SUBJECT: Review of Draft Avian PCB Toxicity Reference Value (TRV)

FROM: Chris Cubbison, Ph.D.
Environmental Health Scientist
National Center for Environmental Assessment (NCEA)

TO: James Chapman, Ph.D.
Ecologist
Region 5

Thank you for the opportunity to comment on the draft Avian PCB Toxicity Reference Value (TRV). I have reviewed the TRV and associated methodology and find the approach to be scientifically reasonable. The approach taken in deriving the TRV should be reasonably protective of birds which are highly sensitive to PCB toxicity. Furthermore, the endpoint selected as the basis for the TRV, reproductive and developmental toxicity, is ecologically relevant and occurs at lower concentrations than most other endpoints. Exposure standards based upon the Avian TRV should be protective of most other exposed birds.

Many of the question that came to mind were answered in the Background to the Charge (which I read later). I highly recommend that you include text from the Charge in the TRV document. Your detailed explanations of the rationale for the conventions used in deriving the TRVs are essential to understanding what was done and why they are the best alternatives.

Charge Questions:

1) Comparison of similar studies via the data normalization procedure is one of several approaches but yours is probably the best for very small data sets.

2) No relevant comments

3) I have seen those effect levels used in other ecological risk assessment without causing a firestorm of protest. Relatively gross effects are often required to cause an observable effect in field populations. A 75% effect level seems reasonable.

4a) Given the limitations of using a single study to derive a TRV, it would seem to be sound policy to interpret the data conservatively. Limiting the interpolation to the linear portion is a reasonable approach.

4b) No relevant comments

4c) When treatment response is greater than the control response, two things come to mind. Either small doses of PCBs confer some survival advantage to the offspring **or** that the data are so variable that you can't tell one point from another. I would attempt to determine possible explanations for the effect before dismissing (not adjusting) the low dose effect. If highly variable results can't otherwise be explained, I would hesitate to use them. (See further comments below)

4d) Lack of CIs is one consequence of using a single study and no access to original data.

5) Given your limited data set, I really like how you dealt with the issue of the greater toxicity following longer exposure. I haven't seen it done before but is seems reasonable and does fit the observed data.

6) Being a pragmatist, I appreciate having to come up with solutions to thorny problems with very limited data. Given the few comparable studies that you had to work with, your options are limited. For years, we developed References Doses for human exposure based upon a single, 'best' study (with supporting studies). It worked pretty well but a consequence was the requirement for high Uncertainty Factors and the potential for gross overprotection. Eventually, we developed techniques such as the Benchmark Dose for using the information in multiple studies and the methods to make the studies more comparable. i.e. The information in multible, somewhat comparable, studies results in less uncertainty and lower UFs. We need to work toward developing methods for combining similar study results to make better use of limited data.

7) TRVs were derived for specific Arochlors with consideration of preference for chronic exposure studies and multi-generation and multi-year exposures. I have read the discussions on the rationale for not requiring statistical significance as a selection criterion. I also understand some of the limitations introduced by the effect of dose spacing and that the lack of statistical significance does not negate the potential for significant toxicity. But if the variability between treatments is so high that you can't distinguish between them statistically, they should at least show a significant trend. I would be more sanguine if several studies could be combined in a meta-analysis for trend and the significance of the slope.

8) You make a good case that, for individual Arochlors, there are insufficient studies for a meta-analysis. So be it. But we should be working toward making TRVs based on single studies a thing of the past. Issues such as weathering (see below) argue for a TEQ approach. Either from a mixtures approach or congener analysis. The issue of how the

TEFs were derived is not that difficult. For most of the laboratory studies, used in our dioxins dose-response analysis, we converted the doses of specific congeners to TEQs based upon the WHO (van den Berg, et al. 1998) and Agency TEFs (U.S. EPA. 2002) for wildlife.

9) Another issue is the selection of specific Arochlors (rather than total PCBs or specific congeners) upon which to base a TRV. There is a discussion about the relevance of a TRV for Arochlor 1254 following weathering and environmental compartmentalization. The end result could be more or less toxic than the parent PCB mix. Additional complexity is added if other Arochlors are part of the mix. Since PCBs are among the several dioxin-like compounds that exert much of its toxic effect via Ah-receptor binding, TRVs based on the level of Ah-R activity in the relevant media avoid the uncertainties of weathering and complex mixtures.

10) Another approach, using the toxicological equivalence of Ah-R binding is the Hazard Index Approach for mixtures that act by similar mechanisms. Since the TRV approach involves specific Arochlor analysis, identification of specific PCB congeners would allow addition of their toxicological equivalents and comparison with some reference standard. I recommend you discuss alternatives to your method for deriving the TRV in the text of the document.

My editorial comments are few. I recommend changing the way you present the no-effect and low-effect TRVs. I suggest the following example (page #1; paragraph #4): "The dietary TRVs for A1242 are 1.3 and 1.4 mg/kg for live kit production (no-effect and low-effect, respectively), adjusted for ....." This confusing notation appears throughout the document.

Finally, it is not clear from your citation (Leonards, et al. 1995)(Table 2) in your discussion of response normalization (page #3; paragraph #1) that you are referring to a methods citation rather than data which might appear in Table 2.

I hope that these comments are helpful and I would be happy provide further information if you have any questions or need additional input. I can be reached at 513 569-7599 or at cubbison.chris@epa.gov.

Cited references

U.S.EPA. 2002. Framework for Application of the Toxicity Equivalence Methodology for Polychlorinated Dioxins, Furans and Biphenyls in Ecological Risk Assessment - External Review Draft. National Center for Environmental Assessment, Risk Assessment Forum. Www.epa.gov/ncea/raf

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[Note added: Peer review comments by Tala Henry]

Peer Review Charge for Mink and Chicken PCB Toxicity Reference Values Derived Through an EDx (effective dose) Procedure

Charge Questions

Peer Reviewers should comment on the following:

1) Is the data normalization method (relative response = treatment response / control response) appropriate for combining the results of different toxicity studies into single dose- or exposure-response plots? If not, what would be a more appropriate method? Explain.

▸The relative response normalization is appropriate so long as the treatment response and control response are from the same study (i.e., same dosing regimen). As for combining results of different studies, see response to 2).

2) Is the linear interpolation method appropriate for deriving the dose or dietary concentration corresponding to selected effect levels? If not, what method would be more appropriate for use with mean data (when the underlying replicate data are not available)? Explain.

▸The combining of data from different studies is only appropriate if the data are "the same" with regard to exposure dose metrics (i.e., for this method to be valid apples can only be combined with apples, not with oranges). For example, dosing or exposure regimens (i.e., route and time) must be similar or identical among all studies to be included (only way to exclude response differences that are due to pharmacokinetic factors). This need for consistency in dose metrics is why the reason behind development of *standard* toxicity testing protocols used in conjunction with the WET methodology.

▸This lack of consistency in dosing regimens is why this type of approach is typically not applied to mammalian/bird wildlife toxicity data or laboratory rodent toxicity data. For example, IRIS toxicity values are generally based on a selected "best" study and adjusted using weight of evidence from other studies because, at least in part, it is inappropriate to combine data due to inconsistencies in dosing regimens. It is worth noting here that during development of the GLWQI wildlife criteria, U.S. EPA (via contractor) explored the possibility of constructing dose-response curves and interpolate EDx values to derive benchmark doses from existing mammalian and bird wildlife Hg and PCB toxicity data. PCB toxicity studies were assembled and reviewed. The pilot PCB analysis used individual dose-response studies (Platonow & Reinhard 1973 data for bird and Bleavins, Aulerich & Ringer, 1980 for mink) presumably for reasons discussed above regarding combining data and included confidence intervals. This cursory analysis did not result in a better estimate of a concern level than the use of the LOAEL determined in the studies. The large confidence interval at the lower doses resulted in interpolated BMD values that were similar to the LOAELs, but with greater uncertainty. It was concluded that to effectively utilize dose-response data and interpolation approaches, it would be necessary to produce appropriate dose-response data for the endpoint(s) of concern. From a quick look at the studies examined for

your effort, there have not been new studies suitable for this analysis (most of the same studies were examined in both efforts.)

3) Are the effect levels appropriate (75 % relative response for low effect, 100 % relative response for no effect)? If not, what effect levels would be more appropriate. Explain.

▸This cannot be judged with the information provided. The value chosen appears to be arbitrary. No scientific rationale or justification is given for selecting the 25% effect level. Selection of the 25% adverse effect level based on the WET program guidance is clearly not applicable here because the WET guidance is designed to support compliance with AWQCs, which are derived to protect aquatic COMMUNITIES. Information should be provided that indicates whether 25% pup or embryo mortality would be expected to adversely affect the populations of mink or bird(s) associated with the site.

4) Are the following modifications of the linear interpolation method recommended for effluent toxicity testing in the Water Program appropriate? If not, how should the method be applied? Explain.

a) Restricting interpolation to the linear portion of the data plots.
▸OK. This is a statistical approach issue, not specific to WET methods.

b) Use of log-linear interpolation in place of (arithmetic) linear interpolation.
▸OK. This is a statistical approach issue, not specific to WET methods.

c) No adjustment when treatment response exceed control responses (relative response allowed to exceed a value of 1.0).
▸In performing dose-response modeling, the shape/slope of the curve is obviously determined by the data, both the associated concentration and response ranges. Care should be taken not to "overweight" the dose-response curve with no effect data, i.e. too many zero responses (RR $\geq$ 1) can affect ECx values.

d) No confidence interval estimation.
▸NO. This is a major shortcoming of this approach. Not having any sort of confidence interval prevents any sort of assessment as to whether this approach is any better than the NOAEL/LOAEL approach and/or best professional judgement. If no "benefit" (i.e. less variability; less uncertainty, etc.) of this approach can be demonstrated why go through all these mathematical gyrations?

▸Original data are often available from study authors. Where study authors contacted for data? If not, acquiring the data would go far in improving this effort (i.e., confidence intervals may be calculated, see part d below).

5) Regarding the mink TRVs only, is the procedure for adjusting the TRV based on exposure during a single breeding season to derive a TRV protective for continuous exposure through two breeding seasons or two generations of females appropriate? (The single-season Aroclor TRVs

are adjusted by multiplying by the mean ratio of the 2-season or generation TRVs divided by 1-season TRVs from feeding studies with field-contaminated prey or Clophen A50.) If the procedure is not considered appropriate, are there any recommended alternative approaches? Explain.

▸I do not think this approach, as presented, is appropriate. Scientifically defensible rationale for making this adjustment are not provided. What are the reasons (i.e. toxicological mechanisms) that the 2-season/field-contaminated studies yielded more toxicity? The approach used implies it is simply time (i.e., cumulative dose is greater in the two season study, hence the adjustment is essentially a sub-chronic to chronic adjustment), but it is not clear that this is the primary reason for the difference. A plausible reason for the increased adverse effects in the second year studies is the presence of other contaminants in the field-contaminated prey. At least two of the two season studies are confounded by the presence of contaminants other than PCBs, which is the same reason used elsewhere to exclude data for derivation of the TRV. Hence there appears to be arbitrary application of the "co-contaminant" criteria.

6) Any other comments on the methodology? [optional]

▸TRVs are derived for several different Aroclors and apparently specific TRVs will be selected for use based on Aroclors detected at a specific site. In implementing such an approach it should be recognized that there are major uncertainties associated with 'defining' Aroclors present at a given site, and that selection of a specific (single) Aroclor TRV for use in the risk assessment perpetuates this uncertainty. Generally, PCBs often cannot be adequately described by reference to Aroclors due to the subjective assignment of congener and response factors. Aside from these analytical uncertainties, there is great uncertainty associated with the assumption that Aroclors are representative of weathered PCB profiles. Together, these factors present major uncertainties associated with the nature and extent of PCB exposure in the risk assessment. To be selective in characterizing effects based on exposure data with such uncertainties may add significant additional uncertainty (i.e., to 'select' a single Aroclor TRV to use in effects characterization, based on very uncertain exposure characterization–single Aroclor). Perhaps it would be prudent to calculate risk estimates using each of the Aroclor TRVs and present a range of potential risk estimates which represent the potential variance in the PCB profiles present.

Other Comments (not related to peer review charge questions) [submitted by Tala Henry].

Background:
I would suggest that the rationale for pursuing Aroclor-based TRVs focus on the fact that Aroclor data is what is available. This is a real-world and legitimate reason, whereas the arguments against using the toxicity equivalence methodology (for dioxin-like PCBs only; see below) are not compelling because they are not based on fact.

First, while it is true that TEFs (i.e. consensus values derived from the WHO expert meeting; van den Berg et al., 1998) may be based on a variety of endpoints (e.g., tumor promotion, early life stage mortality, cytochrome P450 induction, structural similarity), the WHO TEF values are order of magnitude estimates of the relative potency of various dioxin-like chemicals that are appropriate for use in risk assessment. This conclusion is based on expert opinion derived from several workshops in which consensus TEFs have been characterized as presently the most scientifically credible approach available for assessing the cumulative effects of dioxin-like PCDDs, PCDFs and/or PCBs. The U.S. EPA and other international governments continue to embrace this scientific consensus in as much as they have adopted the methodology for risk assessment and risk management purposes (U.S. EPA, 1987; 1989; 2000; 2001; 2003; NATO, 1988a,b; Kutz et al., 1990; Yrjänheiki, 1992)

Second , while it is true that the only way one may apply TEFs and the toxicity equivalence methodology is if congener-specific data are available, it is not true that congener-specific data need be available to determine a TCDD-equivalent concentration (TEQ or TEC) in a particular sample (i.e., tissue, media, etc.). Bioassay-derived TEQs are useful in screening efforts to determine presence of dioxin-like chemicals and give an estimate of the total concentration (i.e., TEQ or TEC). In addition, TEQ or TEC based dose-response relationships may also be useful for determining effects levels (i.e. TRVs), see Tillett et al., 1996.

Third, the comments regarding the H4IIE based assays make it appear that a thorough understanding of the application of such tools for assessing mixtures of PCDDs, PCDFs and/or PCBs is lacking. The H4IIE bioassays are designed to determine TEQs in a sample and/or determine relative potencies values (e.g., TEFs) of individual congeners. In the former application, one determines the TEQ in a sample(s) based on a TCDD curve, in the same cells and under the same conditions (i.e., same solvent). In the later application, it is true that the relative potency values obtained for a given PCDD, PCDF or PCB congener has been found to vary depending upon the solvent used to dissolve the chemicals. However, this is a discrepancy between various sets of TEF values and would be something to consider when selecting which TEF set to use in your assessment, but it does not bear upon comparability between calculated TEQs and bioassay derived TEQs because either type of TEQs would be compared to TCDD dose response curves for determination of potential for adverse effects.

Regarding point 5) of your background discussion:
First, you mis-represent the assumptions inherent in the toxicity equivalence approach. Most egregiously, it is stated that "the key premise of the TEQ approach is that the effects of PCBs are primarily due to aryl hydrocarbon (AhR)-mediated processes (dioxin-like effects)." This is absolutely not true. While the dioxin-like effects of PCBs and/or the dioxin-like PCB congeners have been most well studied, it incorrect to assert that scientists involved in PCB research think or assume that 1) all PCBs are dioxin-like, which is clearly recognized as not being the case, given that criteria are set forth for inclusion of specific PCBs in the toxicity equivalence approach (i.e., specific structural and biological criteria have always had to be met in order for a PCB congener to be included in the toxicity equivalence approach (Barnes et al., 1991; Ahlborg et al., 1994; van den Berg et al., 1998) and thus, the toxicity equivalence approach only covers the 12 "dioxin-like" PCB congeners; see van den Berg, et al. 1998 for details regarding inclusion criteria), or 2) that all toxicity of a PCB mixture is solely attributable to dioxin-like congeners, which is clearly not the case as demonstrated by international efforts currently

underway to assess the relative toxicity of dioxin-like and non-dioxin-like PCBs (WHO, 2001).

Policy Question:
I wonder if or how the presented TRV derivation has been considered within the context of the Great Lakes Water Quality Initiative? Given that the GLWQI criteria are National standards (i.e., issued by EPA as 'rule-making'), derived under the auspices of international treaty with Canada (international implications?), and the water body in question (i.e., Kalamazoo River) is within the Great Lakes Watershed, would the GLWQI criteria be ARARs? Although the GLWQI criteria are for water, they were derived based on selection of TRVs (test dose is the terminology used in the GLWQI criteria documents), deemed "appropriate" via stakeholder input, extensive peer review and public comment. Has any consideration been given to how the proposed variance in TRV (e.g., LOAEL is 2X higher and NOAEL is 10X higher for mink) will be justified to stakeholders in the GLWQI process (e.g., Region 5 water program; Great Lakes States & Tribes; EPA Office of Water; Government of Canada)?

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[Note added: Peer review comments by Dale Hoff]

Peer Review Charge for Mink and Chicken PCB Toxicity Reference Values Derived Through an EDx (effective dose) Procedure

Background

Continuing Need for Aroclor-based TRVs

Although congener-specific analyses are recommended for assessing risks to PCBs, Aroclor-based toxicity reference values (TRVs) are still needed for several reasons. 1) The PCB database at many sites is predominantly or solely Aroclor data. This is especially true of historic data. 2) At contentious sites, the lengthy process for resolving disagreements has resulted in a need to finalize Aroclor-based risk assessments initiated prior to the current emphasis on congener-based approaches. In these situations, abandonment of the an Aroclor approach will entail substantial delay and cost for resampling media and biota to provide synoptic congener data. 3) There is a larger database available on the ecotoxicological effects of PCBs on an Aroclor basis as compared to a dioxin toxic equivalent (TEQ) basis. 4) The utility of the TEQ-based ecotoxicological studies is also compromised by the use of inconsistent toxic equivalency factors (TEF). Conversion to a common TEQ basis is feasible only if the original congener data is reported so that the TEF scheme of choice can be applied, but the underlying congener data are rarely reported in journal articles–further reducing the pool of useable TEQ studies. Studies based on bioassay TEQs, such as the HII4E rat hepatoma cell line, cannot be directly compared to calculated TEQs, and the bioassay results vary with the choice of solvent for dosing the cells. 5) The key premise of the TEQ approach is that the effects of PCBs are primarily due to aryl hydrocarbon receptor (AhR)-mediated processes (dioxin-like effects). Although AhR-mediated effects are frequently reported to be more sensitive endpoints compared to non-AhR effects, it is not clear how generally this relationship applies across taxa and endpoints. In the absence of a non-AhR TEF scheme, an Aroclor-based assessment can provide an indication whether significant non-AhR effects may have been missed in a TEQ-based assessment.

One of the criticisms of Aroclor-based assessments is that the results are more variable compared to TEQ-based assessments. However, in one such comparison by Leonards, et al. (1995), no distinction was made between different Aroclors or Clophens (total PCB vs. reproductive effects in mink was unfavorably compared to TEQ vs. reproductive effects). This comparison was biased since different Aroclors or Clophens differ in their toxicity.

NOAEL/LOAEL Approach

A widely used approach for determining TRVs depends on two statistically-based thresholds: the no observed adverse effect level (NOAEL), which is the highest dose tested that did not result in a statistically discernible effect compared to the control, and the lowest observed adverse effect level (LOAEL), which is the lowest dose that resulted in a statistically discernible adverse effect. Shortcomings in this approach have been long recognized–the main one is that the NOAEL and

LOAEL are affected by factors unrelated to toxicity. An obvious factor is that the TRVs can only be selected from the particular doses used in an experiment (commonly the tested doses are an order of magnitude apart so there are large gaps in the data). Second, statistical significance is not solely determined by toxicity, but also by the statistical power of the study. This has two implications: 1) studies performed with low statistical power will result in higher TRVs compared with studies with high statistical power for the same chemical and receptor, and 2) since the TRVs are statistically defined, the level of adverse effects associated with the NOAEL or LOAEL varies greatly between studies (for example, statistically-derived NOAELs may be associated with adverse effects in as much as 50 % of the test organisms). A related consideration is that this approach acts as a disincentive for improving the quality and statistical power of industry-funded toxicological testing since less rigorous studies are less expensive and have low statistical power that results in higher and less protective TRVs.

EDx or ECx Approach

An alternative is to use the data from toxicological studies to develop dose- or exposure-response relationships, and to use the relationships to determine the no-effect and low-effect doses or exposures that correspond to selected effect levels. This frees the analysis from the specific doses used in a study (a TRV can now be interpolated between the tested doses), and from the non-conservative bias of tests with inadequate statistical power. This approach is referred to as EDx or ECx (effective dose or concentration; x represents the selected effect level of concern).

An example of the ECx approach is in the recommended procedure for analyzing the results of effluent toxicity testing in the USEPA water program (the low effect concentration is defined as the EC_{75}, that is, the concentration that corresponds to a 25 % decrement in response compared to controls).

Work Product

The TRVs for Aroclors have been revisited in Region 5 for application in Superfund sites in which congener data is not available, and for supplemental use to accompany TEQ-based assessments in sites with congener data. Recently, derivation of Aroclor-based TRVs by taking the geometric means of no or lowest observed adverse effect levels (NOAEL or LOAEL), respectively, from selected studies was challenged for including studies with field-contaminated prey that may be confounded by the effects of co-contaminants. The work products under review are the result of combined analysis of studies that reported the reproductive effects of feeding commercial PCB products to mink and chicken.

The effluent toxicity testing guidance in the water program (e.g., Klemm, et al. 1994; Chapman, et al. 1995) was modified for deriving PCB TRVs from multiple chicken and mink studies. 1) The results of the various studies were normalized so they could be compared on a common basis (the guidance is written for interpreting the results of a single experiment in contrast to the multiple mink or chicken studies performed by different researchers that are analyzed for the PCB TRVs). The normalization was accomplished by dividing each mean treatment response by

the respective mean control response. The resulting relative responses are plotted on semi-log graphs (log dose or concentration vs. relative response). The plots showing interpretable dose-response relationships are used to derive the no- and low-effect TRVs by a linear interpolation between the treatments that bracket the effect level of concern. 2) Interpolation is only performed when the effect level of concern falls within the linear portion of the dose-response plot (to avoid uncertain interpolations). 3) A log-linear interpolation is used since it gives a better fit within the linear portion of the data plots compared to the linear interpolation in the guidance. 4) Data are not adjusted when treatment responses exceed control responses (relative responses > 1), since the recommended procedure applies to the results of single, not multiple studies. 5) The procedure for deriving confidence intervals is not implemented since the only available data from the published mink and chicken studies are the treatment means (the underlying data for the individual replicates were not presented for any of the studies).

An alternate approach would be to fit curves to the data, and use the non-linear regressions to calculate the low-effect levels. This approach was not used because only the treatment and control mean responses are reported in the published literature. The underlying replicate data, which would provide the best basis for curve-fitting and are necessary for calculating confidence intervals, are not available.

An additional modification was made for the mink TRVs only. Three studies have shown dramatic increases in adverse effects following continuous exposure to PCBs over 2 breeding seasons or 2 generations of females compared with exposure in 1 breeding season. These studies used field-contaminated prey, or Clophen-supplemented feed, so the 2-season or 2-generation results cannot directly be used to interpolate 2-season or generation Aroclor TRVs. Instead, the 1-season Aroclor TRVs are multiplied by the mean ratio of the available 2-season or generation TRVs divided by the corresponding 1-season TRVs to derive Aroclor TRVs protective for sustained occupancy of a site by female mink.

Literature Cited

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Peer Review Charge

The peer review charge is to evaluate the methodology for deriving Aroclor TRVs. The charge does not include review of the input data (although documentation of the data and the specific sources is included in the materials provided to reviewers), but the methodology for normalization of the data is part of the charge.

Charge Questions

Peer Reviewers should comment on the following:

1) Is the data normalization method (relative response = treatment response / control response) appropriate for combining the results of different toxicity studies into single dose- or exposure-response plots? If not, what would be a more appropriate method? Explain.

This is only appropriate if experimental design portions of the multiple studies are similar. One would NOT want to normalize multiple data sets if one exposure route is of oral exposures by gavage method vs. the other of a contaminated diet. Also, the duration of exposure needs to be similar if not identical. Finally, different strains of organisms can vary in their response. In the example used above with the AWQCs, the organisms used for testing are of known health. This is established as positive control tests are run simultaneously with actual tests using reference toxicants such as KCL. The reference toxicant result (e.g. LC50) must be within a certain percentage of the species mean LC50 for the rest of the test to be valid. Aquatic organisms have always been easier to combine data sets in the way these authors suggest just from the standpoint of assumptions of consistent exposure and duration when an organism is submersed in water are much more robust than when one makes the same assumptions for terrestrial wildlife vertebrate toxicological studies. I believe a much more prudent approach would be develop the dose-response curves (relative response = treatment response / control response; absolutely the way to go) for each study and then use a statistical representation of all the studies (ie, geomean of EC20s).

2) Is the linear interpolation method appropriate for deriving the dose or dietary concentration corresponding to selected effect levels? If not, what method would be more appropriate for use with mean data (when the underlying replicate data are not available)? Explain.

I would generally support the authors proposed use of the interpolation method. However, I have significant misgivings about NOT being able to include confidence bounds. Have the authors of this document attempted to reach the primary authors of the literature. Many times the raw data can be obtained from the original authors to help finish the analysis. Without including the confidence bounds on the dose-response curves, many of the same appropriate arguments presented in this paper which object to the use of NOAELS and LOAELS will apply in the interpolation method as well. For example, if the confidence limits are large, a NOAEL could be

more useful than an EC20 that ranges accross multiple doses in the experimental design.

3) Are the effect levels appropriate (75 % relative response for low effect, 100 % relative response for no effect)? If not, what effect levels would be more appropriate. Explain.

How was the 25% relative response determined to be the critical threshold for the WET program? Was this a science-based or risk-based decision, or one of a question of statistical rigor? The WET program tests principally fat head minnows and ceriodaphnia dubia. Essentially, 3 of 10 individuals from several replicates have to die before a violation under a permit would be issued to the waste treatment operator. I see absolutely no direct correlation with between the testing procedures in the WET protocols and what the authors propose here. The ecologically relevent percent response would be specific to the organism and the endpoint being tested. In other words, I would view 25% pup mortality in mink much more influential on sustaining a population of mink, compared to the influence on an entire aquatic community existing in waters that presented a 25% *in vitro* ceriodaphnia mortality (ceriodaphnia always being one of the more sensitive species in the community).

4) Are the following modifications of the linear interpolation method recommended for effluent toxicity testing in the Water Program appropriate? If not, how should the method be applied? Explain.

a) Restricting interpolation to the linear portion of the data plots.

b) Use of log-linear interpolation in place of (arithmetic) linear interpolation.

This is probably the best. See additional recent guidance RAGS 3 and chapter 4 of the probalistic guidance to help choose best models. There is actually a mink example.

c) No adjustment when treatment response exceed control responses (relative response allowed to exceed a value of 1.0).

d) No confidence interval estimation. No, see comment above

5) Regarding the mink TRVs only, is the procedure for adjusting the TRV based on exposure during a single breeding season to derive a TRV protective for continuous exposure through two breeding seasons or two generations of females appropriate? (The single-season Aroclor TRVs are adjusted by multiplying by the mean ratio of the 2-season or generation TRVs divided by 1-season TRVs from feeding studies with field-contaminated prey or Clophen A50.) If the procedure is not considered appropriate, are there any recommended alternative approaches? Explain.

I would say no. Again, the core of the problem would be the comparibility of the field-

contaminated prey vs. the laboratory mixture of Aroclors exposed in the 2 generation study. I would generate an average ECx of the two studies after one year and compare that to the same ECx after 2 years. If they are signifcantly different, reduce the corresponding dose of the average ECx after one year to be equal to that of the corresponding dose at the appropriate ECx after 2years.

6) Any other comments on the methodology? [optional]

Due Date

October 21, 2002

Format

Electronic submittal to chapman.james@epa.gov, WordPerfect is preferred, version 9 or lower. In case anyone want to submit a spreadsheet as part of the comments, Lotus123 is preferred, version 9.5 or lower for Windows.

Point of Contact

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Subject: Comments on "Peer Review Charge for Mink and Chicken PCB Toxicity Reference Values Derived Through an EDx (effective dose) Procedure"

To: James Chapman
Region V

From: Mark D. Sprenger
OERR-ERTC

Thank you for the opportunity to review the materials you developed on the TRV derivation for PCBs for mink and avian receptors. Overall, I believe the derivation which you conduct is a significant step forward in our ability to formally and objectively interpret the data within the literature.

I have included the charge questions followed by my response to this issue raised in each charge. I have also included, after the responses to the charge questions, some brief observations which may be of some assistance in the future.

Charge Questions

Peer Reviewers should comment on the following:

1) Is the data normalization method (relative response = treatment response / control response) appropriate for combining the results of different toxicity studies into single dose- or exposure-response plots? If not, what would be a more appropriate method? Explain.

I do not believe that there is any reason for concluding that the normalization approach used is invalid. The only criticism which may be valid is that with limited data sets the normalization may skew the results, however, that interpretation is relative to alternate data evaluations and does not inherently mean it is incorrect.

2) Is the linear interpolation method appropriate for deriving the dose or dietary concentration corresponding to selected effect levels? If not, what method would be more appropriate for use with mean data (when the underlying replicate data are not available)? Explain.

I do not see any technically valid reasons for discounting the approach used.

3) Are the effect levels appropriate (75 % relative response for low effect, 100 % relative response for no effect)? If not, what effect levels would be more appropriate. Explain.

I defer to others on this issue. I see nothing technically incorrect and personally believe that the approach used has benefits, as being statistically significant does not inherently mean it is important. I can see this approach being criticized as being a means to increase a TRV (or be less protective), however I do not see this as being inherently true.

4) Are the following modifications of the linear interpolation method recommended for effluent toxicity testing in the Water Program appropriate? If not, how should the method be applied? Explain.

a) Restricting interpolation to the linear portion of the data plots.

b) Use of log-linear interpolation in place of (arithmetic) linear interpolation.

c) No adjustment when treatment response exceed control responses (relative response allowed to exceed a value of 1.0).

d) No confidence interval estimation.

I believe the answer to these questions is simply that I do not see anything which is incorrect or violates some assumption; however I would defer to others on this issue. Relative to confidence intervals, I am not sure that there is even an option, given the limited data sets available.

5) Regarding the mink TRVs only, is the procedure for adjusting the TRV based on exposure during a single breeding season to derive a TRV protective for continuous exposure through two breeding seasons or two generations of females appropriate? (The single-season Aroclor TRVs are adjusted by multiplying by the mean ratio of the 2-season or generation TRVs divided by 1-season TRVs from feeding studies with field-contaminated prey or Clophen A50.) If the procedure is not considered appropriate, are there any recommended alternative approaches? Explain.

I believe approach used is valid and a significant improvement in the formal evaluation of the toxicity data. Certainly, time dependent exposure is an important factor in the response of organisms, and long term accumulators, like PCBs, should be evaluated in this manner or a similar one.

6) Any other comments on the methodology? [optional]

Overall, I believe the approach taken is valid and a significant improvement in the formal and objective interpretation of the literature toxicological information.

General observations:

If the opportunity presents itself for revision of the materials provided it would be useful to present all of the concentrations and exposures in one set of units, currently there is some mixing which creates a little extra mental work for the reader.

In future evaluations I suggest that we are open to the inclusion of gray literature in the evaluation of TRVs, I believe that the original gray literature (e.g. thesis or study report) could provide greater insight into the best interpretation of the data generated by the study.

MEMORANDUM

DATE: October 17, 2002

SUBJECT: Comments on The Recommended Mink and Avian PCB Toxicity Reference Values

FROM: Glenn W. Suter II
Science Advisor

TO: James Chapman, Ph.D.
U.S. EPA
Region V (SR-J6)

Below are my comments on the recommended mink and avian PCB toxicity reference values.

General Comments

Dr. Chapman is to be commended for basing the TRVs on the dose-response relationships rather than hypothesis testing statistics (i.e., on biological significance rather than statistical significance). The conventional NOAELs and LOAELs are statistically indefensible, and the method presented here is a clear improvement.

My primary objection to these documents is the lack of clear and complete presentation of the methods and their underlying assumptions. Specifically, the following points need clarification.

- TRVs are derived for a single Aroclor for each taxon (1254 for mink and 1248 for birds). Are they meant to represent all PCBs, some subset of the Aroclors, or just those particular Aroclors?

- If the TRVs are assumed to be representative of PCBs in general, are they thought to represent average PCBs, the most toxic PCBs, or more toxic than average PCBs (i.e., conservative values)? How were the representative Aroclors selected? Evidently they are not necessarily the lowest.

- How are the TRVs to be applied to a site with reported concentrations of multiple Aroclors or of Arochlors that do not have TRVs?

- How are uncertainties and variances treated? A factor is used to correct for differences between single and multi-year exposures but not for other uncertainties. There are scattered discussions of this issue, but no coherent treatment.

- Is the mink TRV applicable to other mustelid species or to all mammalian species?

- Evidently, the chicken TRV is meant to apply to all birds. It is the most sensitive species tested, but that sensitivity is used to justify not using a factor to account for anticonservative aspects of the TRV. Does that mean that the target is a TRV for bird species of average sensitivity?

- What is the basis for the selection of ED_{75} as the low effect level? I assume that it is intended to be equivalent to typical LOAELs, but that is not stated.

- The TRVs are derived from one of several test endpoints. How was that selection performed and by what criteria? Evidently is was not simply the most sensitive endpoint.

- The formula for interpretation should be presented in the methods section, and the parameters and their units should be defined.

- The method for combining multiple studies should be stated. That is, do you interpolate between points from different studies? Would you interpolate between points in one study for the low effect level and another study for the no effects level?

- "The Saginaw data are included for comparative purposes..." That is a good idea. What are the results of the comparison?

It is always important in scientific writing to be sufficiently clear that a reader or user can readily understand what was done and what the factual and logical bases were. That is particularly important when a somewhat nonstandard method is used.

Responses to Charge Questions

1) Yes, the normalization to controls is appropriate.

2) Linear interpolation is an acceptable method. However, I would not rule out the fitting of a function just because the data for replicates are not available. They are not available for calculating the variance on the interpolated estimates either. While you can not estimate the inter-replicate variance, that may not be the most important concern. I would say that in this analysis you are more concerned about the inter-study variance, which you could capture in the confidence intervals on fitted functions.

3) Acceptability of a level of effect is a policy judgement, but the basis for the choice of 75% is

not stated. If the basis is consistency with past Agency practices, then the level chosen for the low effect level is reasonable. That is, LOAELs established by hypothesis testing are often equivalent to approximately a 25% decrement in performance. At the other end, no decrement in response is certainly equivalent to no effect.

4a) It is not clear how this restriction was applied. Looking at the plots, the transition from nonlinear to linear segments is unclear. This is a matter of judgement, but I would be inclined to drop this restriction. I do not believe that nonlinearity between dose levels is a significant source of error relative to other assumptions involved in TRV derivation.

4b) Distributions of toxic responses are typically more similar to log normal than normal distributions. Therefore, the log-linear interpolation is appropriate.

4c) This issue depends on whether it is believed that the greater-than-control responses are due to random variance or due to a hormetic effect. The smoothing recommended by Klemm et al. is consistent with the former. The interpolation is consistent with the latter. I recommend that the author review the PCB literature for evidence of hormesis. That is, is improved performance typical of low exposure levels in vertebrates? If so, the interpolation is correct. If not, smooth the data.

4d) The bootstrap method to calculate confidence intervals on interpolations presented by Klemm et al. is not applicable to this data set, since the data for responses of replicates are not available. I do not know of any other method that would be applicable.

5) Since there seems to be a consistent increase in effects over time, it is appropriate to adjust for it. The simple method used here is reasonable, and I do not believe that the available information could support a more sophisticated method.

6a) This is not a criticism, but rather a point to consider. The conventional TRVs have two values because of the peculiarities of hypothesis testing based test endpoints. The NOAEL is nominally a no effect level and the LOAEL is nominally a significant effect level. Hence, the threshold from no effects to potentially significant effects must lie somewhere in between. If you are using a biological effects level, there is no need for a two-valued TRV. You could simply choose an effects level as the threshold.

6b) The figures are very hard to read when printed. Also, it would be easier for the reader to judge the reasonableness of the TRVs if they were marked on every plot (e.g., with vertical dashed lines). It would also make the methods clearer if you indicated on the figure from which the TRVs were derived, the points between which you interpolated (e.g., by connecting them with a line).

cc: D. Tucker

Other Comments (not related to peer review charge questions).

Comments by Tala Henry, USEPA, 10/31/02
Responses by James Chapman, USEPA,11/1/02

Background:
I would suggest that the rationale for pursuing Aroclor-based TRVs focus on the fact that Aroclor data is what is available. This is a real-world and legitimate reason, whereas the arguments against using the toxicity equivalence methodology (for dioxin-like PCBs only; see below) are not compelling because they are not based on fact.

> That's a bit strong, Tala. While we disagree on one fact (whether all bioassays produce similar total TEQs since each is calibrated to TCDD), most of our differences stem from considering different aspects of the application TEQ methods. Also, I am not arguing that the TEQ approach shouldn't be used. My point is that like every other risk assessment tool, it has limitations and complications. I don't believe our understanding is sufficiently advanced to exclude other approaches for assessing PCB risk (see examples below). My preference is to assess risk on the basis of both TEQ and total PCB.

First, while it is true that TEFs (i.e. consensus values derived from the WHO expert meeting; van den Berg et al., 1998) may be based on a variety of endpoints (e.g., tumor promotion, early life stage mortality, cytochrome P450 induction, structural similarity), the WHO TEF values are order of magnitude estimates of the relative potency of various dioxin-like chemicals that are appropriate for use in risk assessment. This conclusion is based on expert opinion derived from several workshops in which consensus TEFs have been characterized as presently the most scientifically credible approach available for assessing the cumulative effects of dioxin-like PCDDs, PCDFs and/or PCBs. The U.S. EPA and other international governments continue to embrace this scientific consensus in as much as they have adopted the methodology for risk assessment and risk management purposes (U.S. EPA, 1987; 1989; 2000; 2001; 2003; NATO, 1988a,b; Kutz et al., 1990; Yrjänheiki, 1992)

Second , while it is true that the only way one may apply TEFs and the toxicity equivalence methodology is if congener-specific data are available, it is not true that congener-specific data need be available to determine a TCDD-equivalent concentration (TEQ or TEC) in a particular sample (i.e., tissue, media, etc.). Bioassay-derived TEQs are useful in screening efforts to determine presence of dioxin-like chemicals and give an estimate of the total concentration (i.e., TEQ or TEC). In addition, TEQ or TEC based dose-response relationships may also be useful for determining effects levels (i.e. TRVs), see Tillitt et al., 1996.

> But bioassay-derived TEQs do not necessarily correspond to the results of applying a consensus TEF scheme. More to the point, if I have a calculated TEQ using the WHO-TEFs for PCBs (and maybe dioxins/furans if I have a more comprehensive database), I cannot directly compare this to a H4IIE-derived TRV since the latter may include the effects of other AhR-inducing chemicals besides PCBs, dioxins, and furans. If these other chemicals were present in my samples, but not analyzed and not included in my TEQ calculation, I would be underestimating risks if I compare my calculated TEQ to a bioassay TRV that was affected by additional contaminants not included in my TEF list. At Saginaw, half of the bioassay TEQ was reportedly not accounted for by the combined effect of PCBs, dioxins and furans (Table 2 in Tillitt, et al. 1996).

Third, the comments regarding the H4IIE based assays make it appear that a thorough understanding of the application of such tools for assessing mixtures of PCDDs, PCDFs and/or PCBs is lacking. The H4IIE bioassays are designed to determine TEQs in a sample and/or determine relative potencies values (e.g., TEFs) of individual congeners. In the former application, one determines the TEQ in a sample(s)

based on a TCDD curve, in the same cells and under the same conditions (i.e., same solvent). In the later application, it is true that the relative potency values obtained for a given PCDD, PCDF or PCB congener has been found to vary depending upon the solvent used to dissolve the chemicals. However, this is a discrepancy between various sets of TEF values and would be something to consider when selecting which TEF set to use in your assessment, but it does not bear upon comparability between calculated TEQs and bioassay derived TEQs because either type of TEQs would be compared to TCDD dose response curves for determination of potential for adverse effects.

The same concern over unmeasured contaminants potentially affecting bioassay results that are not included in the available TEF scheme and/or not measured at the site applies here. The cause of the bioassay/calculated TEQ discrepancy at Saginaw is unknown (Giesy, et al. 1997 reported PCNs, PCDTs, or PCDEs could not account for it). Elsewhere, Kannan, et al. (2000) reported that "contribution of PCNs to sum TEQs in fishes from the Detroit River was similar to or greater than those contributed by coplanar PCBs".

The claim that any bioassay result should give the same overall result since each is calibrated to TCDD with its particular solvent is only true if each solvent delivers a similar relative pattern of congeners to the cell. It's not true if different solvents deliver different relative patterns of congeners to the cell (from the same contaminant source). Using Tillitt, et al. (1996) as an example, according to your claim, a DMSO H4IIE bioassay should indicate approximately the same total TEQ as an ISO H4IIE bioassay (for the 20 % carp diet, the ISO value is 40.0 pg/g - their Table 2). Tillitt, et al. (1996) then applied their ISO H4IIE REPs (called TEFs in the publication) to the dioxin, furan, and coplanar PCB analytical data to calculate a TEQ (total of 20.5 pg/g for the same treatment), with half of the measured TEQ unaccounted for. But if I apply the DMSO H4IIE REPs for dioxin, furans, and coplanar PCBs (Clemons, et al. 1994 and 1996) to the same analytical data, the calculated total TEQ is 33.6 pg/g, with only a 16 % discrepancy with the measured TEQ (and Clemons, et al. report fewer REPs than Tillitt, et al. do). Both outcomes cannot be valid.

This leads to another issue. Tillitt, et al. (1996) used the H4IIE REPs to allocate the toxicity among chemicals. When I challenged the allocation at Saginaw (PCBs contributing only 25 % of the calculated TEQ and 12 % of the total bioassay TEQ (their Table 2, 20 % carp diet)), and specifically questioned the order of magnitude lower H4IIE REPs for some key PCB congeners with the ISO solvent compared to those reported for DMSO, Giesey said that the other work was flawed because they did not properly calculate the REPs (didn't characterize the REP over multiple points across the entire dose-response range) and emphasized there is a right and wrong way to make the calculations. When I pressed him on the procedure used for the REPs used for the Saginaw studies, he admitted they were not calculated according to the "right" procedure, either. In any case, by comparison, use of the DMSO REPs indicate that coplanar PCBs account for 70 % of the total calculated TEQ and 59 % of the bioassay TEQ. The ISO REPs indicate that PCBs are a minor player at Saginaw, the DMSO REPs indicate PCBs are the major risk driver at the site. The DMSO results are more consistent with the results of using I-TEFs, in which coplanar PCBs account for 80 % of the calculated TEQ, and 85 % of the measured TEQ (their Table 8).

Comparison of the Saginaw dose-response plots for hatchability (hens fed Saginaw carp) with hen feeding studies with Aroclors shows that PCBs appear to be a sufficient explanation for the Saginaw study (no unexplained toxicity). Conversely, there is an order of magnitude greater effect in the Saginaw study for chick deformity compared to Aroclor studies. Although the results of the Saginaw mink studies show greater toxicity than Aroclor feeding studies, the difference is not the order of magnitude predicted by use of the ISO REPs, but is more in line with the results of applying the DMSO REPs. I am skeptical of the validity of the H4IIE REPs

used by Giesey and do not trust their use for apportioning toxicity and identifying drivers.

In short, this does indicate that, as you put it, "a thorough understanding of the application of such tools for assessing mixtures of PCDDs, PCDFs and/or PCBs is lacking". I'm not saying there is no understanding, but, as for many of the tools used in risk assessment, we always could stand to know more than we presently do, and do well to keep in mind we probably haven't thought of all the questions we should.

Regarding point 5) of your background discussion:
First, you mis-represent the assumptions inherent in the toxicity equivalence approach. Most egregiously, it is stated that "the key premise of the TEQ approach is that the effects of PCBs are primarily due to aryl hydrocarbon (AhR)-mediated processes (dioxin-like effects)." This is absolutely not true. While the dioxin-like effects of PCBs and/or the dioxin-like PCB congeners have been most well studied, it incorrect to assert that scientists involved in PCB research think or assume that 1) all PCBs are dioxin-like, which is clearly recognized as not being the case, given that criteria are set forth for inclusion of specific PCBs in the toxicity equivalence approach (i.e., specific structural and biological criteria have always had to be met in order for a PCB congener to be included in the toxicity equivalence approach (Barnes et al., 1991; Ahlborg et al., 1994; van den Berg et al., 1998) and thus, the toxicity equivalence approach only covers the 12 "dioxin-like" PCB congeners; see van den Berg, et al. 1998 for details regarding inclusion criteria), or 2) that all toxicity of a PCB mixture is solely attributable to dioxin-like congeners, which is clearly not the case as demonstrated by international efforts currently underway to assess the relative toxicity of dioxin-like and non-dioxin-like PCBs (WHO, 2001).

Your response supports the point I am making. When I do a TEQ-based analysis, I've covered what we understand about potential dioxin-like effects. The present TEQ procedure does not include congeners that act through non-AhR-mediated effects. Hopefully some day we'll understand enough to have multiple TEQs that address multiple causal pathways. I don't know of one I can use today at my sites. I should clarify the sentence to state: "the TEQ approach available at present addresses only AhR-mediated processes (dioxin-like effects)". I made no statements whatsoever regarding what "scientists involved in PCB research think or assume" or any claim that "all PCBs are dioxin-like". My statement refers only to what our present TEQ approach accomplishes–it does not address non-AhR-mediated effects (except possibly in an indirect way if the dioxin-like congeners happen to covary with toxic congeners that do not bind with AhR). I used the word "primarily" to reflect the conclusions of a comparison of dioxin-like and non-dioxin-like effects of PCBs:

> "Toxic effects due to coplanar PCBs occur at relatively smaller concentrations than those due to non-dioxin-like PCBs and therefore the TEF approach derives [they meant "drives"] the risk assessment of PCBs... TEQs derived for dioxin-like effects are the critical parameters for the risk assessment of PCBs, that is, the least concentration of total weathered PCBs would be allowed based on the presence of TEQs." (Giesey and Kannan 1998).

The statement that "the key premise of the TEQ approach is that the effects of PCBs are primarily due to aryl hydrocarbon (AhR)-mediated processes (dioxin-like effects)" is an accurate summary of this comparison. The present TEQ procedure wouldn't be used if we knew that it was a minor contributor to toxicity compared to non-dioxin-like effects. We do recommend its use because dioxin-like effects occur at lower exposure levels compared to the non-dioxin-like effects in most of the situations in which they have been compared. But we do not know enough to state with certainty that dioxin-like effects *always* occur at lower exposure levels than do the non-dioxin-like effects.

Policy Question:
I wonder if or how the presented TRV derivation has been considered within the context of the Great Lakes Water Quality Initiative? Given that the GLWQI criteria are National standards (i.e., issued by EPA as 'rule-making'), derived under the auspices of international treaty with Canada (international implications?), and the water body in question (i.e., Kalamazoo River) is within the Great Lakes Watershed, would the GLWQI criteria be ARARs? Although the GLWQI criteria are for water, they were derived based on selection of TRVs (test dose is the terminology used in the GLWQI criteria documents), deemed "appropriate" via stakeholder input, extensive peer review and public comment. Has any consideration been given to how the proposed variance in TRV (e.g., LOAEL is 2X higher and NOAEL is 10X higher for mink) will be justified to stakeholders in the GLWQI process (e.g., Region 5 water program; Great Lakes States & Tribes; EPA Office of Water; Government of Canada)?

Actually, the GLI mink dietary LOAEC is 3X higher than the one I interpolated. The GLI mink LOAEC is based on a treatment whelping frequency of 29 %, survival at birth of only a single live, but underweight pup, and zero kit survival after a few days. Regardless of who reviewed the GLI, this is an inappropriate LOAEC for risk management. Unlike Superfund in which risk is assessed over the NOAEL-LOAEL range, the GLI is based only on no-effect levels. I could not in good conscience use a LOAEC that is expected to result in 100 % kit mortality. The GLI mink NOAEC is a default 0.1 LOAEC. The NOAEC I propose is also estimated, but is informed by the general shape of the exposure-response plots.

At the site I am now working on, we have to address contaminated sediments. We could make EqP calculations to derive protective sediment values consistent with the GLWQI water criteria (for the NOAEC estimate), but I doubt it would be defensible since the only site-specific information would be sediment TOC. We'd also have to model the relationship between sediment pore water conc. and surface water conc. for the different reaches, and assume that the GLI assumptions hold for our site.

GLI modeled bioconcentration by fish and bioaccumulation through trophic levels. The rivers we are addressing do not necessarily have the same fish or trophic structure, and are likely to exhibit bioconcentration/bioaccumulation patterns that differ from the GLI models. That's why we measure fish (or other prey) accumulation, and empirically derive sediment-to-fish BAFs to derive site-specific preliminary remedial goals. I would be hard-pressed to defend the GLI foodchain and accumulation assumptions at every PCB site I work on.

The avian TRV I've developed from chicken is nearly identical with the GLI avian PCB TRV based on pheasants taking into account the interspecific extrapolation factor of 3 used by the GLI (and no such factor in my analysis since chickens are more sensitive than the few other avian species tested to date).

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Tala Henry
11/01/2002 12:42 PM

To: JAMES CHAPMAN/R5/USEPA/US@EPA
cc: Chris Cubbison/CI/USEPA/US@EPA, Dale Hoff/EPR/R8/US
Glenn Suter/CI/USEPA/US@EPA, Mark Sprenger/ERT/R2/USEPA/US@
Subject: Re: FYI - Additional Comments and Responses

Jim,
I think you took my comments in a vein that they were not intended (i.e., advisarial). The main reason commented on aspects of the TEF methodology was that the way the background section is written gave me the impression of a lack of understanding of some aspects of the methodology...perhaps it is really just a lack of clear and complete presentation (as G.Suter referred to). So, I spent the time to comment in order to give you an opportunity to change some of the text prior to releasing to persons outside the Agency who are very familiar with the methodology. For example, in response to one of my comments you suggest that a sentence be modified...this is exactly the type of response I envisioned "fixing the problems". Your responses indicate you have spent some time mulling over the TEF methodology. While in some instances we would appear to be disagreeing, I think it is more a matter of not understanding what one another is saying because there are some complicated issues being discussed (e.g., the whole bioassay derived TEFs vs. TEQs issue). In a broader sense, I think we are generally "on the same page" (e.g., I'm no great fan of the bioassay derived TEQs, but they still *may* be useful in certain applications).

I would propose that we discuss some of these issues sometime, as written comments back and forth isn't so amenable to true discussion. Perhaps at the next ERAF meeting?

So, again, I didn't mean for my comments to be construed as an "attack", just thought more information would be helpful in preparing your project for consumption outside the Agency.

Tala

MEMORANDUM

DATE: October 18, 2002

SUBJECT: Response to General Comments from Comments on The Recommended Mink and Avian PCB Toxicity Reference Values, October 17, 2002, Glenn W. Suter II

FROM: James Chapman, Ph.D.
Ecologist

TO: Glenn W. Suter II
Science Advisor

My responses to the General Comments are entered under each comment. The Response to Charge Questions section of the original memo is not included in this one.

General Comments

Dr. Chapman is to be commended for basing the TRVs on the dose-response relationships rather than hypothesis testing statistics (i.e., on biological significance rather than statistical significance). The conventional NOAELs and LOAELs are statistically indefensible, and the method presented here is a clear improvement.

My primary objection to these documents is the lack of clear and complete presentation of the methods and their underlying assumptions. Specifically, the following points need clarification.

- TRVs are derived for a single Aroclor for each taxon (1254 for mink and 1248 for birds). Are they meant to represent all PCBs, some subset of the Aroclors, or just those particular Aroclors?

  Response: TRVs are derived for A1254, A1242, and Clophen A50 for mink; and A1254, A1248, and A1242 for chicken. Since A1242 exhibited two patterns in chicken, one corresponding to A1254, the other to A1248, the chicken TRVs reduce to two: an A1254 type and an A1248 type. The TRVs are Aroclor-specific (or Clophen-specific), but with the recognition that it may be necessary to apply them to other Aroclors to fill data gaps.

- If the TRVs are assumed to be representative of PCBs in general, are they thought to represent average PCBs, the most toxic PCBs, or more toxic than average PCBs (i.e., conservative values)? How were the representative Aroclors selected? Evidently they are not necessarily the lowest.

  Response: The TRVs are Aroclor-specific. Whether a particular TRV is more or less conservative if applied as a surrogate for another Aroclor for which insufficient data are available for TRV derivation depends on the particular pair of Aroclors under

consideration. It seems unlikely that other Aroclors would be more toxic than the Aroclors assessed in this effort (with the exception of A1248 in mink).

There are three criteria for Aroclor selection. One is the availability of published toxicity studies using commercial PCB formulations. This is an unfortunately limited data base, for example, no mink feeding studies were located for A1248. Aroclors were not considered if only a single dose was reported, for example, A1221 and A1268 (Lillie, et al. 1974; Cecil, et al. 1974), since there is no basis for interpolation. Another consideration is the mix of Aroclors detected in biota at the two Region 5 Superfund sites for which this effort is being made. For example, a TRV for A1232 could be derived from Lillie, et al. (1975), but was not since A1232 has not been reported in biota at these sites.

Cecil, H., J. Bitman, R. Lillie, G. Fries, and J. Verrett. 1974. Embryotoxic and teratogenic effects in unhatched fertile eggs from hens fed polychlorinated biphenyls (PCBs). Bull Environ Contam Toxicol 11: 489-495.

Lillie, R., H. Cecil, J. Bitman, and G. Fries. 1974. Differences in response of caged white leghorn layers to various polychlorinated biphenyls (PCBs) in the diet. Poultry Sci 53: 726-732.

Lillie, R., H. Cecil, J. Bitman, and G. Fries. 1975. Toxicity of certain polychlorinated and polybrominated biphenyls on reproductive efficiency of caged chickens. Poultry Sci 54: 1550-1555.

- How are the TRVs to be applied to a site with reported concentrations of multiple Aroclors or of Arochlors that do not have TRVs?

  There are at least three options for addressing multiple Aroclors. Aroclor-specific TRVs could be weighted to reflect the Aroclor mix at a site, the TRV of the predominant Aroclor could be applied, or the TRV of the most toxic Aroclor in the mix could be applied. All approaches have limitations. Mass-weighting is dependent on the uncertainties surrounding Aroclor allocation in analytical samples. The utility of the other two approaches depends on the proportions of the Aroclors detected, and the type of question being asked. For example, if the predominant Aroclor overwhelmingly accounts for the total (say 80 % or higher), it may make sense to go with the predominant Aroclor TRV. If there is a more even mix, use of the most toxic TRV is appropriate for screening, the mass-weighted approach for detailed risk assessment.

  Treatment of Aroclors without TRVs depend on the Aroclor in question. Surrogate TRVs may be applied when similar toxicity is reasonably expected. For example, I would apply the mink A1254 TRV to A1248, but not to A1260.

- How are uncertainties and variances treated? A factor is used to correct for differences between single and multi-year exposures but not for other uncertainties. There are

scattered discussions of this issue, but no coherent treatment.

There is no treatment of variances since the necessary data bases are beyond my reach. The single vs. multi-year or muli-generation exposure difference is addressed because the available studies show that this has a large impact on the results. I am not aware of another treatment variable that has a similarly large effect.

I need to write an uncertainty section for the TRV derivation (the internal consistency of multiple studies within individual scatterplots indicates low uncertainty for outcomes in laboratory settings; but the low number of data points for many of the endpoints raises uncertainty). However, I believe that greater uncertainty is associated with the application of the TRVs in risk assessments than in the derivation of the TRVs. In addition to the usual uncertainties surrounding lab-to-field extrapolations and exposure assumptions, there is an additional uncertainty surrounding the interpretion of weathered/bioaccumulated PCB data as Aroclors.

- Is the mink TRV applicable to other mustelid species or to all mammalian species?

I see it provisionally applicable to otter since controlled reproductive studies have not been performed with otter, but other endpoints indicate that otter may be a sensitive species (Kannan, et al. 2000). The mink TRVs are probably overly conservative for ferrets (Bleavins, et al. 1980). I do not expect the mink TRVs to be directly applicable to other mammals, but, in the complete absence of species-specific toxicity information, would use the mink TRV without interspecific extrapolation uncertainty factors to conservatively assess an unpredictable response in an untested species.

Bleavins, M., R. Aulerich, and R. Ringer. 1980. Polychlorinated biphenyls (Aroclors 1016 and 1242): Effects on survival and reproduction in mink and ferrets. Arch Environ Contam Toxicol 9: 627-635.

Kannan, K., A. Blankenship, P. Jones, and J. Giesy. 2000. Toxicity reference values for the toxic effects of polychlorinated biphenyls to aquatic mammals. Human Ecol Risk Assessm 6: 181-201.

- Evidently, the chicken TRV is meant to apply to all birds. It is the most sensitive species tested, but that sensitivity is used to justify not using a factor to account for anticonservative aspects of the TRV. Does that mean that the target is a TRV for bird species of average sensitivity?

I have no idea what average avian sensitivity to PCBs is–not nearly enough species have been rigorously investigated. I see two options for assessing risk to species without PCB toxicity data: use a tested wild species and apply an interspecific uncertainty factor, or use chicken data without an interspecific uncertainty factor (justified by the high sensitivity of chicken compared to the other species tested to date). Coincidentally, the Great Lakes Initiative approach based on pheasant with an interspecific uncertainty factor is closely

similar to the chicken TRV presented here without an interspecific uncertainty factor.

- What is the basis for the selection of ED_{75} [1] as the low effect level? I assume that it is intended to be equivalent to typical LOAELs, but that is not stated.

  Use of ED_{75} as the low-effect level is adopted from the guidance for evaluating the results of effluent toxicity testing in the Water Program (for example, Klemm, et al. 94; Chapman, et al. 95). I would have no issue using LOAELs if I were confident they generally represent 75 % effect levels–but we know they're all over the board.

  Chapman, G., D. Denton, and J. Lazorchak. 1995. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to West Coast Marine and Estuarine Organisms. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA/600/R-95-136.

  Klemm, D., G. Morrison, T. Norberg-King, W. Peltier, and M. Heber. 1994. Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms, 2nd ed. Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati. EPA/600/4-91/003.

- The TRVs are derived from one of several test endpoints. How was that selection performed and by what criteria? Evidently is was not simply the most sensitive endpoint.

  Again, a couple of factors came into play. An endpoint had to be either reported or calculable from data provided for commercial Aroclor laboratory studies. Results for multiple doses/exposures had to be reported. The scatterplot had to show an interpretable exposure-response relationship, and the target effect level (relative response = 0.75) had to be bracketed by the available data and fall reasonably within the linear portion of the scatterplot. This left me with a limited number of endpoints that could be considered. For example, mink kit bodweight at 6 wk would be a better endpoint for ecological risk assessment purposes, but more data are available for kit bodyweight at birth from commercial Aroclor laboratory studies. The only endpoints consciously dropped from TRV derivation were the mink whelping frequency and total and live kits per whelped dam because all three are integrated in the live kits per mated female endpoint.

- The formula for interpretation should be presented in the methods section, and the parameters and their units should be defined.

  I'm not sure I understand what formula you mean, but agree that the TRV formulas in the notes to Table 1 should be brought into the text and the terms defined.

- The method for combining multiple studies should be stated. That is, do you interpolate

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[1] Note added after the response was sent. The term "ED_{75}" should read "ED_{25}" in both the question and response.

between points from different studies? Would you interpolate between points in one study for the low effect level and another study for the no effects level?

I will add discussion to the paragraph starting "Treatment responses are normalized ... so that multiple studies may be compared on a common basis". Yes to both questions, although to clarify the second–interpolation also may occur between points from different studies when deriving any single TRV as shown in the right column of Table 1 (a TRV is not necessarily interpolated between points from a single study).

- "The Saginaw data are included for comparative purposes..." That is a good idea. What are the results of the comparison?

No formal analysis has been made to date since this does not directly relate to decisions at either site (the statement was to emphasize that the TRVs are not confounded by co-contaminants, an issue raised over the previously proposed TRVs for the sites). But, it is interesting to see how the allocation of the contributors to the total bioassay H4IIE-TEQ compares to the relative toxicity of the Saginaw studies to commercial Aroclor studies. According to Tillitt, et al. (1996), the non-ortho and mono-ortho congeners contributed only 17 to 25 % of the total calculated TEQ (dioxins and furans contributing the rest) (based on H4IIE TEFs applied to congener analysis of fish samples), but the H4IIE bioassay TEQs for fish samples were 54 to 95 % higher than the TEQs calculated from analytical data and H4IIE TEFs (their Table 2). Giesey believes the extra TEQ is from polychlorinated naphthalenes (not analyzed at Saginaw). This means that the PCBs themselves should be contributing only 11-13 % of the toxicity due to consumption of Saginaw fish (calculated from their Table 2). This is clearly not the case for egg hatchability, for which the Saginaw results are consistent with those of A1248 and one set of the A1242 results (my Figure 1, Saginaw is shown as "PCB"). In contrast, the ED_{75} for chick deformity occurs at an order of magnitude lower than either A1242 or A1248 (my Figure 15–Saginaw ED_{75} about 0.11 mg/kg-d, and the Aroclor ED_{75} greater than 1.1 mg/kg-d), consistent with the TEQ allocation for Saginaw fish. The mink studies do not support the TEQ allocation at Saginaw. The results of the Saginaw mink studies do not plot at an order of magnitude lower than the Aroclor studies (I have not prepared combined plots yet).

Tillitt, D., R. Gale, J. Meadows, J. Zajicek, P. Peterman, S. Heaton, P. Jones, S. Bursian, T. Kubiak, J. Giesy, and R. Aulerich. 1996. Dietary exposure of mink to carp from Saginaw Bay. 3. Characterization of dietary exposure to planar halogenated hydrocarbons, dioxin equivalents, and biomagnification. Environ Sci Technol 30: 283-291.

It is always important in scientific writing to be sufficiently clear that a reader or user can readily understand what was done and what the factual and logical bases were. That is particularly important when a somewhat nonstandard method is used.

Agreed.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 5

DATE: March 6, 2003

SUBJECT: Toxicity Reference Values (TRVs) for Mammals and Birds Based on Selected Aroclors

FROM: James Chapman, Ph.D., Ecologist

TO: Shari Kolak, RPM

1 Summary

Toxicity reference values (TRVs) are developed for polychlorinated biphenyl (PCB) mixtures based on studies of controlled exposures to commercial Aroclor products for sensitive mammal (mink) and bird (chicken) species. The TRVs are interpolated from dose-response plots of Aroclor exposure and reproductive or growth endpoints, with data collated from multiple studies. The interpolated low-effect level is the dose that results in a 25 % decrease in an endpoint response compared to that of the control group, and the interpolated no-effect level a 10 % decrease.

The TRVs are recommended for mink or conservative application to bird species that lack species-specific PCB toxicity data. Since the TRVs are derived from studies of sensitive species to PCBs, use of uncertainty factors for extrapolation to other species is not recommended. The TRVs are given as bodyweight normalized doses (mg PCB per kilogram bodyweight per day) for ingestion by birds to facilitate application to bird species of different sizes. Dietary TRVs (mg PCB per kg food) on a wet weight (ww) basis are given for mink since interspecific extrapolation is not necessary to assess risk to wild mink. The TRVs for bird eggs are given as the concentration in whole eggs on a wet weight basis (mg PCB per kilogram egg).

The TRVs are summarized in Table 1. See the text for details.

Table 1. Interpolated PCB Toxicity Reference Values (TRVs) Based on Controlled Exposures of Mink and Chicken to Commercial PCB Products.

Commercial PCB Product (Aroclor)	Mink Diet [a]		Bird Dose		Bird Egg	
	mg/kg ww		mg/kg_{BW}-d		mg/kg whole egg ww	
	no effect	low effect	no effect	low effect	no effect	low effect
1242	1.3	1.4	0.1 - 0.5 [b]	0.4 - 0.8 [b]	1.0	1.5
1248	see 1254 [c]	see 1254 [c]	0.4	0.5	0.7	1.3
1254	0.5	0.6	0.6	1.2	9	12

Notes for Table 1:

a) Mink TRVs are adjusted for continuous exposure over multiple years or generations at the same site (see text).

b) Two response patterns are exhibited in the published studies, which are separately assessed (see text).

c) A1248 has not been tested in mink. The mink A1254 TRVs are applied because A1248 is as potent as A1254 in an *in vitro* mammalian bioassay (Tillitt, et al. 1992).

The TRVs for mink are adjusted for continuous exposure through two breeding seasons or generations because mink feeding studies with one of the European commercial PCB formulations (Clophen A50) and, independently, with field-contaminated fish have shown pronounced increases in toxicity compared to exposure over a single breeding season. The A1254 TRV is based on the number of live kits per mated female and kit bodyweight at birth. Although kit survival following birth might be a more sensitive endpoint compared to live kit production or kit bodyweight at birth (see Clophen A50 below), the data are insufficient for determining kit survival TRVs for A1254, other than to state that the low-effect dietary concentration is less than 1 mg/kg for a single season of exposure. Surprisingly, no mink feeding studies were located for A1248. However, A1248 is as potent as A1254 in an *in vitro* [1] mammalian bioassay (Tillitt, et al. 1992), so the A1254-based TRVs are applied to A1248. The TRVs for A1242 are based on live kit production. Data are insufficient for other endpoints for A1242.

For comparison, the mink dietary TRVs for Clophen A50, one of the European commercial PCB products, over 2 seasons exposure are 1.1 to 1.3 mg/kg for live kit production (no effect to low effect), 2.3 mg/kg for kit bodyweight (low effect), and less than 0.8 mg/kg for kit survival (low effect). Data are insufficient to determine no effect TRVs for the latter two endpoints, other than to state that the no effect TRVs are greater than the control dietary concentration of 0.01 mg/kg.

All of the TRVs from chicken studies are based on hatchability, the most frequently reported endpoint of PCB studies with chicken. Chick bodyweight is a less sensitive endpoint in the few cases for which comparisons can be made with hatchability. Chick survival appears to be a more sensitive endpoint than hatchability in the sole available comparison (low effect TRV of 0.3 mg/kg_{BW}-d for A1248), but is less reliable compared to the A1248 hatchability TRV because the survival TRV is based on sparser data requiring interpolation over a much wider dose gradient.

A1242 exhibits two dose-response patterns in chicken studies–one with TRVs somewhat lower than A1248, and another approaching the A1254 TRVs. The two A1242 patterns may be due to differences in A1242 batches, chickens, feed, or experimental designs. Instead of choosing between the two patterns, both sets of A1242 TRVs are shown.

TRVs calculated from exposure to commercial PCB products may underestimate the toxicity of PCBs in the field because of environmental weathering and selective retention in biota that alter the proportions of dioxin-like congeners compared to the source product. Concurrent exposures to other chemicals in the field that contribute to dioxin-like toxicity reduces the margin of exposure to PCBs that can be tolerated without exhibiting adverse effects. Use of the lower of the TRVs given above is recommended to account for increased toxicity due to these effects (A1254 TRVs for mink and A1248 TRVs for birds). The TRVs are probably not applicable to sites with source

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[1] The literal meaning of *in vitro* is "in glass", which refers to experiments performed outside of a living body, for example, in test tubes , petri dishes., or other laboratory apparatus. In this case, the bioassay measures the response of cultured cells to PCBs and other chemicals with dioxin-like toxicity.

PCBs different from the Aroclors assessed in this effort, for example, A1260, which is less toxic than A1242, A1248, or A1254 in an *in vitro* mammalian bioassay (Tillitt, et al. 1992).

The methodology used for deriving the TRVs was internally peer-reviewed by USEPA scientists. The peer review charge included review of the data normalization procedure for combining the results of different studies, effect size selection, linear interpolation method (including the following modifications–restriction of interpolation to the linear portion of the data plots, use of log-linear interpolation, no adjustment for violations of monotonicity for hormetic responses, and lack of confidence interval estimation), and adjustment of mink TRVs for increased toxicity associated with continuous exposure over 2 breeding seasons or 2 generations. The peer reviewers also made additional comments regarding meta-analysis, uncertainty associated with Aroclor approaches, TEQ as an alternative approach, and editorial comments. The peer review comments and responses are summarized in Responses to Peer Review Comments, Wildlife PCB Toxicity Reference Values. March 6, 2003. USEPA Region 5 Superfund Division, Chicago. The present version of this work product has been revised in accordance with these comments and responses.

2 Acronyms

A1242, A1248, A1254, A1260 - different Aroclors (commercial PCB products produced in America)
A50 - one of the Clophen commercial PCB products produced in Europe
AhR - aryl hydrocarbon receptor (cellular protein that binds with dioxin-like chemicals in the initial step of a cascade of interactions leading to expression of toxic effects)
AWQC - federal ambient water quality criteria
BMF - biomagnification factor (= concentration in animal / concentration in food or environmental media)
BW - bodyweight
Ca^{2+} - calcium ion
d - day
EC_x - effective concentration resulting in a treatment response x % less than the control response
ED_x - effective dose resulting in a treatment response x % less than the control response
fw - fresh weight (weight including moisture content at the time of measuring)
g - gram
GLI - Great Lakes Initiative
H4IIE - designates a particular cultured rat cell line used in an *in vitro* bioassay for dioxin-like activity
I-TEF - international toxic equivalency factors
kg - kilogram (1000 g)
LD_{50} - lethal dose to 50 % of the exposed population
LOAEL - lowest observed adverse effect level (lowest tested dose that caused a statistically discernible response compared to the control group)
LOEC - lowest observed effect concentration (lowest tested concentration that caused a statistically discernible response compared to the control group)
lw - lipid weight (concentration on a lipid (fat) basis, e.g., mg PCB per kg fat)
mg - milligram (0.001 g)
pg - picogram (one trillionth gram)
NOAEL - no observed adverse effect level (highest tested dose that did not cause a statistically discernible response compared to the control group)

NOEC - no observed effect concentration (highest tested concentration that did not cause a statistically discernible response compared to the control group)
OECD - Organization for Economic Co-operation and Development (Europe)
PCB - polychlorinated biphenyl
ppb - parts per billion (equal to 0.001 ppm)
ppm - parts per million (equal to mg/kg)
ppt - parts per trillion (equal to 0.000001 ppm or pg/g)
PRG - preliminary remedial goal
REP - relative potency (the fractional response of a dioxin-like chemical compared to 2,3,7,8-TCDD in a particular test or approach)
RR - relative response (normalized treatment response = treatment response / control response of the same study)
TCDD - tetrachlorodibenzo-*p*-dioxin
TEF - toxic equivalency factor (the consensus fractional response of a dioxin-like chemical compared to 2,3,7,8-TCDD based on variety of research approaches and results)
TEQ - toxic equivalent concentration (the concentration of 2,3,7,8-TCDD that is expected to equal the potency of a mixture of dioxin-like chemicals, calculated by multiplying the concentrations of each dioxin-like chemical by their respective TEFs, or measured directly by an *in vitro* bioassay)
TRV - toxicity reference value (the concentration or dose of a chemical used to assess risk–no effect TRVs are not expected to cause adverse effects, and low effect TRVs are the levels at which adverse effects first become apparent)
USEPA - United States Environmental Protection Agency
WHO - World Health Organization
wk - week
ww - wet weight (weight including the normal moisture content)

3 Background

One of the issues raised concerning the Baseline Ecological Risk Assessment for the Allied Paper, Inc./Portage Creek/Kalamazoo River Superfund site concerns the appropriate PCB TRVs for wildlife. Inclusion of studies performed with field-contaminated prey from Saginaw Bay, MI, in the derivation of PCB TRVs for mink and birds was criticized because the observed effects may have been confounded by contaminants other than PCBs.[2] One of the alternatives suggested in written and oral comments was to use the TRVs developed for the Great Lakes Initiative (GLI) water quality criteria (WQC) for wildlife (USEPA 1995a). This was looked into, but a difficulty occurred in attempting to apply the TRVs used by the GLI to Superfund purposes.

The GLI WQC are based solely on the no observed adverse effect level (NOAEL), but the guidance for Superfund ecological risk assessments recommends evaluation of risks and calculation of site-specific preliminary

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[2] Whether PCBs appear to be major or minor contributors to the observed toxicity in the Saginaw Bay studies depends on which set of toxic equivalency factors (TEFs) are used to convert the measured contaminant data to dioxin toxic equivalents (TEQs). PCBs are the major contributor according to the International TEF (I-TEF) scheme, but are minor contributors according to the TEFs [better termed relative potencies (REPs) because they are based on a single experimental approach] reported for the H4IIE bioassay (an *in vitro* assay performed with a rat hepatoma cell line) (Tillitt, et al. 1996; Geisey, et al. 1997). The I-TEF scheme has been replaced by World Health Organization TEFs (WHO-TEFs) (Van den Berg, et al. 1998), but the new scheme does not significantly alter the outcome.

remedial goals (PRGs) for both the NOAEL and lowest observed adverse effect level (LOAEL) (USEPA 1997). At first this did not appear to be problematic since the GLI reported both the available NOAELs and LOAELs of the studies reviewed for calculating the WQC. The issue in applying these TRVs for Superfund use is that the GLI did not evaluate the appropriateness of the LOAEL data for regulating LOAEL-based risks. The mink assessment represents an extreme example. The LOAEL chosen by the GLI for mink reproduction resulted in complete kit mortality–only 2 of 7 exposed females whelped (gave birth), producing only 1 live but underweight kit that died before reaching 4 weeks age (Aulerich and Ringer 1977). Since a NOAEL was not identified in this study, the LOAEL was converted to a NOAEL by dividing by an uncertainty factor of 10 (USEPA1995a). The calculated NOAEL was equivalent to the NOAEL of a mink feeding study performed with field-contaminated fish, which indicated that the conversion provided an adequate margin of safety for ensuring no adverse effects (USEPA 1995a), and therefore satisfied the objectives of the GLI WQC. However, at the LOAEL, zero successful reproduction is not an adequate representation of a lowest adverse effect level, instead it represents the maximum possible adverse effect on reproduction, and therefore does not satisfy the Superfund objectives of characterizing the risk range between no effects and the level at which adverse effects become detectable.

The problem in applying the LOAEL identified by the GLI is inherent in the methodology of the NOAEL/LOAEL approach, which has been criticized in numerous publications (for examples see Crump 1984; Suter 1996; OECD 1998; Crane and Newman 2000). The main limitations of the NOAEL/LOAEL approach are that the values are significantly affected by factors other than toxicity, and the available dose-response information is not utilized. NOAELs and LOAELs are statistically defined–a LOAEL is the lowest tested dose that exhibited a statistically discernible response compared to the control response, and a NOAEL is the highest tested dose that did not show a statistically discernible response from that of the control. An obvious issue is that, by this approach, NOAELs and LOAELs are restricted to the particular doses tested. This is the source of the problem with the GLI selected LOAEL for mink–the lowest treatment dose tested resulted in 0 % successful reproduction, so by default, it was identified as the "lowest" adverse effect level, even though it is obvious that lower doses, if tested, would also show adverse reproductive effects. Also, determination of statistical significance depends not only on toxicity, but also on the study design (the particular dose levels tested and number of replicates per dose) and the particular statistical procedure chosen to compare the treatment and control responses, all of which affects the statistical power of the comparison. An unfortunate result is that "poor" studies with low statistical power are rewarded from the perspective of potentially liable parties because they result in higher (less protective) NOAELs and LOAELs compared with more rigorous and expensive studies with higher statistical power. Similar considerations pertain to the number of dose levels tested–fewer doses are less expensive, but may "miss" appropriate effect levels by wide margins. Another way of considering these issues is that, because of the widely ranging statistical power associated with toxicity tests, and differences in the doses selected for study, the level of adversity associated with statistically determined TRVs varies uncontrollably. For example, in a ring test of aquatic toxicity laboratories, the mean decrease in response associated with the statistically identified no observed effect concentration (NOEC) was about 10 % across laboratories, but ranged as high as 37 % in individual cases (cited in Crane and Newman 2000). In another evaluation, statistically determined no effect concentrations could be associated with as much as 50 % decreases in responses compared to controls depending on the data and the choice of statistical method, leading the investigators to conclude that "the NOEC is rarely if ever an indicator of no effect" (Crane and Newman 2000). The same issues apply to LOAEL determinations. Another limitation of the NOAEL/LOAEL approach is that it does not make use of the available dose-response information. See Crump (1984) for an example showing how statistically determined effect levels can give misleading results for chemicals with markedly different dose-response patterns.

An alternative is to use the data from toxicological studies to develop dose-response relationships, and to use the relationships to determine the no-effect and low-effect doses that correspond to selected effect levels. This frees the analysis from the specific doses used in a study (a TRV can now be interpolated between the tested doses), and from the non-conservative bias of tests with inadequate statistical power. In this approach, the effect size is selected first (effect size is the percentage decrease in performance compared to control), for example, that the low effect level should be a 20 % decrease in treatment response compared to the control response. Then the dose corresponding to the selected effect size is determined from the dose-response relationship. This approach is referred to as "ED_x" or "EC_x", where ED is effective dose, EC is the effective concentration, defined as the dose or "concentration that produces a specified size of effect relative to an untreated control"[3] (Chapman 1998), and x represents the effect size–the selected change in response compared to the control response (for example, the dose resulting in a decrement in response of 25 % is designated as ED_{25}). A particular ED_x (the dose that would result in a decrease in performance by the percentage chosen as the effect size) may be determined from dose-response data through several procedures including graphical techniques, calculation from a fitted equation, or interpolation between the measured responses that bracket the selected effect size. A modification is to calculate the TRV for the lower confidence limit of the data, which is termed a "benchmark dose" (USEPA 1995b).

Some of the advantages of the ED_x approach for determining TRVs are that the size of the effect is known (because it is selected beforehand), the TRVs are not constrained to the particular doses tested (because they are determined from the dose-response relationship revealed by the test data), the TRVs do not depend on the particular statistical test chosen, and confidence intervals can be calculated. One of the main limitations is in choosing the appropriate regression model for curve-fitting approaches. Confidence limits may be quite large for threshold[4] and hormesis[5] models (Chapman 1998). Also, determination of TRVs for very low effect levels (less than ED_{10}) becomes strongly model dependent (Moore and Caux 1997; Scholze, et al. 2001). Fortunately, determination of TRVs for effect levels greater than 10 % has low model dependence, that is, the choice of regression model has relatively minor effects on TRVs when calculated for ED_{10} or higher (Moore and Caux 1997).

An ED_x approach therefore is applied to the PCB toxicity data for mink and chicken to develop TRVs appropriate for assessing the risk range between no effect and low effect levels.

Although congener-specific analyses are recommended for assessing risks to PCBs, Aroclor-based toxicity reference values (TRVs) are still useful for several reasons. 1) The PCB database at many sites is predominantly or

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[3] Dose is the rate of exposure of an animal or plant to a chemical, usually expressed as the amount of chemical per unit bodyweight per day. Instead of dose, the concentration of the chemical under investigation may be given for contaminated media (water, soil, air), food, or in a tissue or the whole body of the exposed animal or plant.

[4] For threshold models, treatment responses are flat (not different from the control response) at low doses until a critical level of dose is reached above which the treatment responses decrease as the dose increases.

[5] Hormesis refers to enhanced responses (treatment responses greater than control responses) at low doses of a chemical that has adverse effects at higher doses. For hormesis, treatment responses are flat (same as control) as the dose initially increases above the control dose, but, before reaching the critical threshold for adverse effects, the treatment responses become greater than the control response. As the critical threshold is approached, the treatment response decreases to the control level, and, as the doses increase above the critical threshold, the treatment responses decrease below the control response (adverse effects occur).

solely Aroclor data. This is especially true of historic data. 2) At contentious sites, the lengthy process for resolving disagreements has resulted in a need to finalize Aroclor-based risk assessments initiated prior to the current emphasis on congener-based approaches. In these situations, abandonment of the an Aroclor approach could entail substantial delay and cost for resampling media and biota to provide synoptic congener data. 3) There is a large database available on the ecotoxicological effects of PCBs on an Aroclor basis. 4) The utility of the available TEQ-based ecotoxicological studies is compromised by the use of inconsistent toxic equivalency factors (TEF). Conversion to a common TEQ basis is feasible only if the original congener data is reported so that the TEF scheme of choice can be applied (Dyke and Stratford 2002), but the underlying congener data are rarely reported in journal articles, which reduces the pool of comparable TEQ studies. Results of *in vitro* bioassay TEQs cannot be directly compared to calculated TEQs because bioassay results and congener relative potencies (REPs) may vary with changes in test protocols, for example, the solvent for dosing the cells (Tillitt, et al. 1991), exposure time (Clemons, et al. 1997), or the species from which the cell line is derived (Aarts, et al. 1995); and bioassays may show responses to chemicals not having significant effects in animals because of toxicokinetic processes not present *in vitro*. 5) The currently available TEQ approach assesses only toxicity related to aryl hydrocarbon receptor (AhR)-mediated processes (dioxin-like effects). Although AhR-mediated effects are frequently reported to be more sensitive endpoints compared to non-AhR effects, it is not clear how generally this relationship applies across taxa and endpoints. In the absence of a non-AhR TEF scheme, an Aroclor-based assessment can provide an indication whether significant non-AhR effects may have been missed in a TEQ-based assessment.

4 Methods

4.1 Linear Interpolation

The effluent toxicity testing guidance in the water program (e.g., Klemm, et al. 1994; Chapman, et al. 1995) is modified for deriving PCB TRVs from multiple mink or chicken studies. The guidance recommends linear interpolation between the treatments showing effects that bracket the chosen effect level. The linear interpolation method avoids the complications associated with selection of the appropriate regression model by focusing on the mean dose-response trend in the region surrounding the chosen effect level. Confidence intervals are then calculated through a bootstrap method. The method assumes monotonicity, that is, that the mean response decreases as the test concentration increases, and data are smoothed (adjusted) if this pattern is violated.

The linear interpolation method was developed for deriving TRVs from the results of individual toxicity studies. However, for the present effort, the results of multiple studies are combined to better reveal the shape of the dose-response relationship for PCBs. This is necessary because most of the individual PCB toxicity studies tested a limited number of doses. Interpolation is strictly implemented for this effort–no extrapolations beyond the empirical data range are performed.

The first modification is to normalize the data so multiple studies can be compared on a common basis. The reason for combining research results is to better define the shape of the dose-response relationship compared to that shown by the relatively low number of doses tested in any single experiment (Section 4.7). Normalization is accomplished by dividing each mean treatment response by the respective mean control response (Equation 1). Two examples of this normalization procedure for combining multiple studies are Leonards, et al. (1995) and Tananka and Nakanishi (2001) (the latter normalized both response and exposure concentration, but only response is normalized for the present effort). The normalized responses are termed "relative response" (RR).

RR = treatment response / control response of the same study [1]

The relative responses are plotted on semi-log graphs (base 10 logarithm dose or concentration vs. relative response). The plots showing interpretable dose-response relationships (Section 6.1.1) are used to derive the no- and low-effect TRVs by a linear interpolation between the treatments that bracket the effect level of concern. The plots showing obviously inconsistent dose-response relationships, either because there is no relationship or because the combined studies are incompatible for some reason, are excluded for TRV derivation.

The second modification is interpolation is only performed when the selected effect size falls within the steep linear portion of the dose-response plot. There are two purposes: 1) the linear interpolation method is applicable to linear responses, but will over- or underestimate for nonlinear portions of the dose-response relationship; and 2) this avoids interpolation over excessively large exposure gradients for which the shape of the dose-response relationship is poorly known. The practical result is that most of the interpolations are performed between relatively small gradients in exposure values. The majority of the TRV interpolations for mink occur between treatments that differ in dietary concentrations by 2-fold or less, with the largest difference for the interpolations for Clophen A50 and live kits (3-fold for exposure over 2 breeding seasons, and 5-fold over 1 breeding season). Interpolation is not performed for the TRV for A1254 and kit survival, for example, because there is a 100-fold difference between the dietary concentrations of the treatments that bracket the target low-effect response. Many of the bird TRVs are interpolated between small gradients (2- or 3-fold for A1242 or A1248 dose and hatchability, less than 4-fold for A1254 dose and hatchability, and 2-fold or less for A1242 or A1254 egg residue and hatchability). A few bird TRVs are interpolated over larger gradients (6- fold for A1242 egg residue and chick bodyweight, 7-fold for A1248 egg residue and hatchability, and 10-fold for A1242 or A1248 dose and chick bodyweight, and A1248 dose and survival). Interpolations are not performed for greater than 10-fold differences in treatment doses.

A third modification is log-linear interpolation (Equation 2) is used since it gives a better fit within the linear portion of the data plots compared to the linear interpolation in the guidance.

$$\text{Log}_{10}\,\text{TRV} = \text{Log}_{10}\,C_j + (((M_1 * P) - M_j) * ((\text{Log}_{10}\,C_{j+1} - \text{Log}_{10}\,C_j) / (M_{j+1} - M_j))) \quad [2]$$
$$\text{TRV} = 10^{\text{Log10 TRV}}$$

Where TRV is the interpolated toxicity reference value, P is the chosen effect size (Section 4.2), M_1 is the control relative response (1.0 by definition because the response data is normalized to controls), C_j is the test concentration of the treatment that produced a relative response (M_j) greater than P, and C_{j+1} is the test concentration of the treatment that produced a relative response (M_{j+1}) less than P. The symbols used in Equation 2 are the same as the ones in the guidance for effluent toxicity testing. Equation 2 is used for interpolating TRVs on the basis of PCB concentration in mink diet or chicken eggs. A similar equation is used for interpolating TRVs on the basis of bodyweight-normalized dose to chicken, where C is replaced by D for dose.

A fourth modification is data are not smoothed when treatment responses exceed control responses (relative responses > 1) to allow for hormesis (enhanced response at very low doses). One of the response patterns used for bird TRV derivation, chick bodyweight vs. A1242 egg residues (Figure 27), was attributed to hormesis by the investigators (Gould, et al. 97). The same investigators also reported a hormetic effect of A1254 on chick bodyweight (Figure 26). Gould, et al.'s conclusion is accepted because hormesis is evident at two dose levels for two different endpoints. All three of the commercial PCB products tested in mink feeding studies show possible

hormetic effects on the number of live kits per mated female (Aroclors 1242 and 1254, and Clophen A50) (Figures 2, 3, 7). Hormesis is evident in the Clophen A50 experiment for exposure durations of both 1 and 2 breeding seasons (Figure 7). This effect is also shown by some of the feeding trials performed with field-contaminated prey for the same endpoint (Figures 8 and 13). Therefore, acceptance of hormetic responses is justified for the effects of egg residues on chick bodyweight (as attributed by the researchers), and the effect of dietary exposure on the number of live kits per mated female mink (exhibited in multiple studies). This indicates that adjustment of deviations in monotonicity is unwarranted for a treatment response exceeding the control response. The same modification to the linear interpolation method to allow for potential hormesis was made in a recent comparison of techniques for calculating effective doses (Isnard, et al. 2001). Data smoothing for monotonicity is performed in a few cases when the treatment responses are less than the control response, that is, when hormesis can not explain the deviations (documented in the notes to Tables 2 and 3).

A fifth modification is the procedure for deriving confidence intervals is not implemented since the only available data from the published mink and chicken studies are the treatment means (the underlying data for the individual replicates were not presented for any of the studies). The bootstrapping method for generating confidence intervals for the linear interpolation method requires the full replicate data.

An additional modification was made for the mink TRVs only. Two mink feeding studies, one performed with Clophen A50-supplemented feed and one with field-contaminated prey, reported the reproductive effects of PCBs associated with exposures over both one and two breeding seasons, and the latter study also reported the reproductive effects in two generations of exposed females. Both studies showed increased adverse effects in the second year or generation of continuous exposure. Since only single-season exposures have been reported for commercial Aroclor feeding studies, TRVs protective for long-term occupancy of a site by female mink are calculated by multiplying the single-season Aroclor TRVs by the mean ratio of the Clophen A50 and field-contamination TRVs for exposure over two breeding seasons or generations divided by the corresponding TRVs for single-season exposure in the same studies (the ratios are given in Table 2).

4.2 Effect Size

Effect size is the amount of decrease in response of animals or plants exposed to a chemical compared to unexposed controls that is selected as the level of concern for assessing risk (the x of ED_x, Section 3). The selected effect sizes for this effort are not based on receptor-specific life history/population models. The bird TRVs, derived from chicken data, are intended to provide conservative TRVs for application to species of unknown sensitivity to PCBs, for which no single population model would be applicable. The mink TRVs may also be applied to mammalian receptors of unknown sensitivity to PCBs (this requires bodyweight normalization of the mink dietary TRVs), in addition to mink for which it is derived. The effect sizes used in this effort are chosen for pragmatic reasons–to minimize model dependence, approximate the power of well-designed toxicity studies, and maintain general consistency in approach with other regulatory uses of toxicity test data. In short, to select a low effect size that is expected to be detectable in a well-designed study, and is reasonably consistent with prior Agency practice. The very steep PCB dose-response plots make the question of the appropriate low effect level somewhat moot, since there is a small range between no-effect and total-effects levels.

A pragmatic consideration is to avoid choosing an effect size for which interpolation may be strongly model dependent. In an examination of aquatic toxicity data sets, Moore and Caux (1997) concluded that interpolation

becomes strongly model-dependent for less than 10 % decreases in response compared to that of controls (see also Scholze, et al. 2001). The various models gave reasonably consistent results for response differences of at least 10 % compared to controls. A related consideration is the effect size commonly associated with statistically-determined lowest observed effect concentrations (LOECs) in well-designed toxicity studies. The LOECs of the toxicity studies for the ambient water quality criteria (AWQC) and pesticide programs generally correspond to 20 to 25 % effect sizes (Suter, et al. 2000), and interpolation of the 25 % effect size is recommended for effluent toxicity testing (e.g., Klemm, et al. 1994; Chapman, et al. 1995). Another pragmatic consideration is consistency with the basis for regulatory decision-making in other programs that utilize toxicity testing results. A *de minimis* effect size of 20 % was identified in one such review (summarized in Suter, et al. 2000) [note: this is not a standard written in the regulations, but the minimum effect size associated with regulatory actions in practice].

This indicates that a reasonably detectable effect size consistent with Agency practices in other programs would fall between 20 and 25 %. The higher of these values is chosen for this effort to ensure that the low effect size represents a non-trivial departure from the control response (equivalent to 75 % relative response). In other words, the interpolated low effect TRV is the ED_{25} or EC_{25}.

The no effect size is set a t 10 % (relative response of 90 %), so the interpolated no effect TRV is the ED_{10} or EC_{10}. Similar to the rationale for the choice of low effect size, 10 % is chosen for no effect size because it is unlikely to be identified as a LOAEL in a reasonably well-designed toxicity study, is lower than the *de minimis* effect-level identified in a review of regulatory decision-making, but is at the minimum size so that the calculated ED_{10} is not strongly model-dependent (various regression techniques will likely give similar values).

The effect sizes could be further refined by linking them to species-specific population models to derive effect levels from projected population dynamics–the models probably need to be both region- and habitat-specific, but even so, there may be significant uncertainty (Section 6.1.6). However, because of the nature of the dose-response relationships for PCBs and reproductive endpoints in mammals and birds, such refinement would have relatively minor impact on the final TRV values.

The question of the appropriate value for the low effect size is made somewhat moot by the very steep dose-response plots for PCBs. For example, the A1248 oral dose to hens associated with complete hatch failure (~1 mg/kg-d) is less than 3 times greater than the dose showing no effect (~0.4 mg/kg-d) (Figure 19). The same is true for mink endpoints. Live kit production is completely suppressed at a dietary concentration of 5 mg/kg A1242, but no effect is reported at 2 mg/kg (exposure over a single breeding season) (Figure 2). The range in A1254 dietary concentrations for the same endpoints are 2 and approximately 1 mg/kg, respectively (exposure over a single breeding season) (Figure 3). Refinements of the effect level will therefore produce only relatively small changes in the TRVs.

4.3 Study Selection

Study results are selected according to the following criteria: 1) studies published in journals (gray literature [6] excluded), 2) primary sources (secondary sources [7] excluded), 3) matched control and treatment responses, 4) continuous PCB exposure up to or through the initiation of breeding (responses following cessation of exposure are excluded if sufficient time elapsed to allow depuration [8] to occur prior to breeding), and 5) treatment responses individually reported by dose and Aroclor (aggregated responses based on combinations of exposure levels or combinations of Aroclors are excluded). The individual Aroclor constraint is not applied to studies with field-contaminated prey. Statistical significance is not a criterion for selection of treatments within a study since the objective is to develop dose-response relationships over the full gradient tested (treatments that do not differ from the control response are as important for delineating the dose-response relationship as the treatments that do differ). When response data are reported for more than one exposure time, data for later exposure periods take precedence over earlier exposure periods or data averaged over the entire exposure period. Data are taken from text, tables, or figures so long as the selection criteria are met.

Only studies in which the test animals were exposed to commercial PCB products are used for calculating TRVs. Studies performed with field-contaminated prey are not directly used for calculating TRVs (to avoid possible confounding effects of contaminants not occurring in PCB products), but are included to contribute to the weight-of-evidence for response trends (e.g., evidence of hormesis), to contribute to the estimation of the proportional change in mink responses when the exposure duration increases from one breeding season to two breeding seasons or generations, and for overall comparison with Aroclor studies. Aroclor and field contamination studies are plotted separately for mink, but since only one chicken study is included with field-contaminated feed, it is plotted on the same graphs with chicken Aroclor studies to conserve space (the field-contaminated study is shown as "PCB" in Figures 17, 21, 25, 26, and 29-31).

Of the studies used for TRV derivation, only one did not continue exposure throughout breeding. Käkelä, et al. (2002) exposed mink to A1242-supplemented food for 21 weeks, but then switched to the control diet at the onset of breeding. This treatment is included because there was no delay between the cessation of A1242 exposure and initiation of breeding, therefore depuration did not occur prior to breeding. The sole TRV calculation involving this treatment is for live kits per mated female for A1242, in which the Käkelä, et al. datum is consistent with the trend of the other studies (Figure 2).

One of the "field-exposed diet" studies (mink fed meat from A1254-exposed cows) reported the control response for only one of the endpoints in the study (live kits per mated female) (Platanow and Karstad 1973). Other responses are included only when the treatment response was zero (e.g., 0 % kit survival in the 0.64 ppm treatment), because the relative response in this case is not affected by the specific value of the control response.

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[6] Gray literature refers to studies not published in journals or books, or abstracts of results that provide insufficient information on methods and data. Examples of gray literature include meeting abstracts, government reports, master's or doctoral theses, unpublished research notes, and prepublication drafts.

[7] Primary sources are to the original publications reporting research results. Secondary sources are review articles, compilations, or other summaries of previously published work.

[8] Depuration is the elimination of chemicals from an animal after the cessation of exposure, through metabolic conversion and/or excretion.

This study is not included in the A1254 TRV derivation because A1254 was not fed directly to mink. The bioaccumulation process in cows increased the toxicity of the PCBs to the next higher trophic level (animals feeding on cows) as does bioaccumulation in wild animals (PCB toxicity to predators is usually greater than to their prey), so this study is included as one of the field-exposure studies.

It is not feasible to exactly match the exposure durations between studies. Exposure durations range from 6 to 14 wk for chicken feeding studies, with most between 6 and 9 wk (Table 7) (an individual 39-wk treatment by Platanow and Reinhart (1973) is not used for TRV derivation), and from 3 to 10 months for mink studies performed over a single breeding season (Table 6) (the results of the 2-month exposure duration by Jensen (1977) is not used for TRV derivation because the type of PCB in this study was not identified). For mink, the studies are segregated by the number of breeding seasons exposure was maintained (the results of exposure over 2 breeding seasons or 2 generations are analyzed separately from 1-season results). The data show no obvious effects due to the range in exposure durations (other than the 1-season vs. 2-season or 2-generation results for mink which are therefore disaggregated) (see Sections 6.1.2 and 6.1.5 for further discussion).

The exposure route for all of the mink studies is the same–contaminated diet. For oral dose to chicken, the exposure route is contaminated diet with one exception–contaminated water in the study by Tumasonis, et al. (1973). The data do not show an effect related to this difference in exposure media. The relative effect due to exposure to contaminated water is consistent with the effect trends of exposure to contaminated diet (Figures 20 and 24). As it turns out, the Tumasonis, et al. results had no direct influence any of the TRV interpolations. For egg concentration, the exposure route was through maternal dietary exposure except for Gould, et al. (1997) in which PCBs were injected into egg yolks on day 0 of incubation. The Gould, et al. study influenced one TRV (chick bodyweight vs. A1242 egg residue). Again, the response trend is consistent between exposure routes (Figure 27) (see Section 6.1.3 for further discussion).

4.4 Toxicity Endpoints

Data for the following reproductive and growth endpoints were collected from a review of mink PCB studies: whelping frequency (number of female mink giving birth / number mated), total kits (live and stillborn at birth) per whelped female, live kits per whelped female (at birth), live kits per mated female (at birth), kit bodyweight, and kit survival (Table 4). Since the effects of the first three endpoints are integrated in the number of live kits per mated female, TRVs are not separately calculated for whelping frequency or for total or live kits per whelped female. Kit bodyweight and survival are reported for various times following birth as given in the original studies. TRVs are calculated for kit bodyweight at birth, but not for later times, because the database for later times is smaller than for bodyweight at birth. Kit survival was reported for 4 to 6 weeks following birth in the studies used for TRV derivation.

For chicken PCB studies, the toxicity endpoints include egg productivity, egg fertility, hatchability, chick bodyweight, chick survival, and chick deformity. To maintain comparability among the dose-response plots (reduced response at higher doses for endpoints exhibiting a relationship with PCB exposure), chick deformity is converted to chick normality, that is, the relative proportion of chicks *without* deformities is plotted. Chick normality is calculated as 1.0 - the proportion of deformed chicks. As with other endpoints, treatment normality is divided by the corresponding control normality to calculate the relative response, in this case, relative normality (or normalized normality!).

4.5 Data Conversions

Normalization of response data is discussed in Section 4.1. The data sources, relative response calculations, and other data conversions are documented in Tables 6 and 7.

The mink dietary PCB concentrations are as given in the original studies when available. Two studies expressed the exposure in terms of daily ingestion (mg PCB/mink/d), instead of dietary concentration (Brunström, et al. 2001; Kihlström, et al. 1992). The dietary concentration is calculated by dividing the daily PCB ingestion by the daily food ingestion reported in each study (see notes to Table 6). For some of the study results, the reported data are converted to make them consistent with the toxicity endpoints assessed in this effort. For example, if the number of live kits per mated female is not given in the original study, it is calculated by multiplying the number of live kits per whelped female by the fraction of females whelped of those mated. The conversions are documented in the notes to Table 6.

The chicken dietary PCB concentrations are converted to bodyweight-normalized doses by multiplying by the food ingestion rate reported in the study, or by a default leghorn hen food ingestion rate of 0.067 kg feed/kg_{BW}-d (Medway and Kare 1959). For the single study with PCB exposure through water (Tumasonis, et al. 1973), the bodyweight-normalized dose is calculated by multiplying the PCB concentration in water by the reported daily water consumption per hen divided by the reported hen bodyweight (see note to Table 7). When egg PCB concentrations were reported for egg yolks, the data are converted to whole-egg concentrations by multiplying by 0.364, the proportion of yolk in chicken eggs on a wet weight basis (Sotherland and Rahn 1987).

The relative "chick" normality (see Section 4.4) for Lillie, et al. (1975) is based on abnormal embryos, not on deformities in hatched chicks. However, data are insufficient for deriving deformity-based Aroclor TRVs. The relative "chick" bodyweight for Gould, et al. (1997) is based on 17-d embryos, not on hatched chicks. This data set plays an important role in the A1242 egg TRVs for chick bodyweight.

4.6 Presentation

The source data, data conversions, and relative response calculations are documented in Tables 6 and 7. The relative responses are summarized in Tables 4 and 5, and plotted in Figures 1-32 in semi-log graphs (dose or concentration on a base 10 logarithmic scale). To aid interpretation, the data points of commercial PCB feeding studies that exhibit interpretable dose-response relationships are linearly connected in the figures showing the effects of a single commercial product (an exception is made for Figures 25 and 28 because of the small number of data points). Data points are also linearly connected in the figures illustrating the Restum, et al. (1998) study performed with field-contaminated diets because the results are used in part to estimate the effect of increasing exposure duration from 1 breeding season to 2 breeding seasons or generations. Data are presented as scatterplots (unconnected) in the figures simultaneously showing the effects of multiple Aroclors or multiple field-contaminated diet studies on an individual toxicity endpoint, and in the figures of endpoints that do not exhibit an interpretable dose-response relationship.

The TRV interpolations are presented in Tables 2 and 3. Although the TRVs are derived through calculation, and not through a graphical approach, their derivation can be visually understood by examining the figures. The low effect size is shown in the figures for endpoints used for TRV derivation by a horizontal line indicating 0.75

relative response (effect size of 25 %). The low effect TRV (ED_{25} or EC_{25}) is represented by the dose or concentration corresponding to the intersection of the 0.75 relative response line and the line connecting the scatterplot data. The two data points nearest to the intersection are the data used for interpolation (see Tables 2 and 3 for the sources and values of the interpolation data). Similarly, a no effect TRV (ED_{10}) is the intersection of the 0.90 relative response line (not shown) and the line connecting the scatterplot data.

4.7 Example

A comparison between the results of individual studies and combined studies is illustrated in Figure 16 for the effect of A1248 dose to hen on hatchability. The 9 mean data points in this plot come from 3 studies–one contributing 4 means, one 3 means, and another 2 means (the exposure durations of these 3 studies are similar, 8 to 9 wk). There is an internally consistent dose-response relationship based on the combined data that exhibits a threshold for significant adverse effects above 0.3 mg/kg_{BW}-d, with a steep decrease in hatchability to nearly complete suppression above 1.0 mg/kg_{BW}-d. Based on the combined data, the interpolated no effect TRV (ED_{10}) is 0.38 mg/kg_{BW}-d, and the low effect TRV (ED_{25}) 0.48 mg/kg_{BW}-d (Table 3). Taken individually, the interpolated ED_{25} for the separate studies are approximately 0.2, 0.25, and 0.45 mg/kg-d. Two of the studies provide inaccurate estimates of the ED_{25} because the doses chosen for those studies do not adequately reveal the steep portion of the dose-response relationship. In both cases, the doses used for interpolation differ by an order of magnitude, that is, interpolation is performed over a 10-fold dose gradient The one study (Lillie, et al. 1975) that adequately reveals the steep portion of the dose-response relationship was performed with closely spaced doses (2-fold gradients) specifically selected between the doses showing no and severe effects in an earlier investigation by the same research group.

Statistical analyses were presented in two studies [9] for the effect of A1248 dose on hatchability. The NOAEL was 0.12 mg/kg_{BW}-d (2 ppm treatment), and LOAEL 1.2 mg/kg_{BW}-d (20 ppm treatment) for Lillie, et al. (1974). Compared to the dose-response relationship in Figure 16, the NOAEL is much lower and LOAEL much higher than the actual threshold for effects. In the study by Scott (1997), the NOAEL was 0.07 mg/kg_{BW}-d (1.0 ppm treatment) and LOAEL 0.67 mg/kg_{BW}-d (10 ppm treatment). In this case, the LOAEL is closer to the ED_{25} of the combined data, but the NOAEL is much lower than the ED_{10}, in other words, one treatment dose was fortuitously chosen that fell within the narrow transition between no and severe effects, but the 10-fold gradient to the next lower dose tested was too large to adequately represent the threshold for adverse effects.

5 Results

5.1 Mink Studies

The results of mink studies are shown in Figures 1-15. Exposure-response relationships are evident for number of live kits per mated female (Figures 1-3, 7, 8, and 13), kit bodyweight (Figures 5, 9, 10, and 14), and kit survival (Figures 11, 12, and 15). Data were also normalized for whelping frequency, total kits per whelped female, and live

[9] Unfortunately, the statistical analyses in Lillie, et al. (1975) were only performed to compare the effects of different Aroclors (with the results of the multiple doses combined for any single Aroclor), or different doses (with the results of multiple Aroclors combined for any single dose). Statistical comparisons were not made to compare the effects of different doses of any single Aroclor.

kits per whelped female, but these effects are integrated in the live kits per mated female endpoint, so are not separately analyzed.

The interpolated TRVs are given in Table 2. The dietary TRVs (mg/kg ww) for exposure in a single breeding season are as follows: A1242–2.5 (no effect) to 2.7 (low effect) for live kits per mated female; A1254–1.0 (no effect) to1.1 (low effect) for live kits per mated female and 1.1 (low effect) for kit bodyweight; and Clophen A50–2.4 (no effect) to 3.1 (low effect) for live kits per mated female. The A1254 TRVs for kit survival cannot be interpolated because of data complications (described below) and, for the no effect TRV, excessively large dose gradients, but are greater than 0.02 and less than 1.0 mg/kg ww diet.

The A1254 relative response for kit survival appears to show a no effect level of 1.0 mg/kg ww (Wren, et al. 1987) and complete mortality at 2.0 mg/kg ww (Aulerich and Ringer 1977) (Figure 6). Although Wren, et al. (1987) show the same kit survival for controls and the 1 mg/kg treatment, they reported a dramatic shift in the cause of the mortality in the two groups–mainly trauma and infection in the control kits (9 of 12 kits that died after birth), but predominantly starvation in the treatment kits (13 of 14 treatment kits that died after birth). In contrast, they reported that none of the control kit mortality was due to starvation. These observations raise the possibility that the treatment mortality might have been related to wasting syndrome, a "starvation-like" syndrome of chemicals with dioxin-like effects (Seefeld, et al. 1984; Lu, et al. 1986). Although the Wren, et al. study does not prove that wasting syndrome occurred, the major shift in the causes of mortality between the treatment and control groups indicates that there is substantial uncertainty in concluding that the 1 mg/kg treatment is, in fact, the no effect dietary concentration for kit survival in the Wren, et al. study. This means that the no effect dietary A1254 TRV for kit survival may be less than 1 mg/kg ww, and greater than 0.02 mg/kg ww (control), but more precise determinations cannot be made with the existing data.

Two studies, one performed with a commercial PCB product (Brunström, et al. 2001), and one with field-contaminated prey (Restum, et al. 1998), reported the reproductive effects of PCBs associated with exposures over both one and two breeding seasons. Restum, et al., also reported the reproductive effects in two generations of exposed females. Both studies showed increased adverse effects in the second year or generation of continuous exposure compared to the first (Figures 7-10, and 12). Brunström, et al. (2001) wrote:

> "In the second season, the effects on reproduction were more pronounced and clearly dose dependent... In our study, the concentration in the feed was the same during the two reproduction seasons, resulting in a reduced frequency of whelping females in the second season only. This finding suggests that the PCB concentration in the animals increased from the first to the second reproduction season, showing the relevance of long-term exposure for estimation of a LOAEL."

Brunström, et al. (2001) fed mink diets spiked with Clophen A50, one of the European commercial PCB products, and reported results for exposure over both 1 breeding season (6 months) and 2 breeding seasons (16 months). This study showed a dramatic decrease in the whelping frequency from 90 % of mated females for the first breeding season to 39 % for the second season in their "A50 high" treatment (2.3 mg/kg ww diet). The control whelping frequency was 93 % in both years. Live litter size per whelping female decreased nearly by half between the two exposure periods for the same treatment (from 3.8 live kits/whelped female the first year to 2.0 the second year) (control values 4.0 and 4.4, respectively). Mean kit bodyweight also decreased for this treatment (from

7.9 g to 6.7 g) (control values 9.6 and 8.9, respectively). Only kit bodyweight was statistically discernible from the control in the first breeding season, but, in addition to kit bodyweight, both whelping frequency and live litter size per whelped female were also statistically discernible from control values in the second breeding season. Sufficient data are available to calculate TRVs for both exposure periods for the number of live kits per mated female [10] (Table 2 and Figure 7). The low effect TRV for exposure over 2 breeding seasons (1.3 mg/kg) is 0.42 of the corresponding TRV for 1 season exposure (3.1 mg/kg), and the 2-season no effect TRV (1.1 mg/kg) is 0.47 of the 1-season value (2.4 mg/kg).

Restum, et al. (1998) fed mink various proportions of field-contaminated carp from Saginaw Bay, Michigan, and reported results for exposures over 1 breeding seasons (6 months), 2 breeding seasons (16 months), or 2 generations (exposure *in utero* [11] followed by 12 months exposure) (Figures 8, 10, and 12). Six comparisons are shown in Table 1 between 1-season and 2-season or 2-generation TRVs for live kits per mated female, kit bodyweight, and kit survival. Note that for live kits per mated female, the ratios of 2-season or 2-generation responses divided by the 1-season response result in maximum ratios. This is because the 1-season live kit per mated female TRV cannot be interpolated (it is at a higher dietary concentration than the highest tested). Instead of making an uncertain extrapolation, the relative response at the highest dietary concentration tested is used for the 1-season low effect TRV (0.9 relative response at 1.0 mg/kg). Since the 1-season EC_{25} is at a dietary concentration greater than 1 mg/kg, the actual product of dividing the 2-season or 2-generation TRVs by the 1-season TRV would be smaller than the ratios shown in Table 1 for live kit per mated female (0.39 and 0.28, respectively). There are no such issues for the other endpoints. Overall, the ratio of 2-season or 2-generation TRVs divided by 1-season TRVs ranges from <0.28 to 0.87 for the various endpoints in the Restum, et al., study (Table 1).

For the purposes of adjusting the single-season Aroclor TRVs so they will be protective for sustainable occupancy by mink for multiple years or generations at a given location, the 1-season TRVs are multiplied by the mean ratio of the 2-season or 2-generation low effect TRVs divided by the 1-season TRVs based on the studies by Brunström, et al. (2001) and Restum, et al. (1998). The mean ratio of the seven comparisons is 0.52, that is, on average, the low effect TRV for 2-seasons or 2-generations exposure is 52 % of the low effect TRV for 1-season exposure to PCBs. Accordingly, the single-season TRVs for A1242 and A1254 are multiplied by 0.52 to derive TRVs for long-term sustainability. By this approach, the A1254 low effect TRV is 0.6 mg PCB/kg ww diet for live kit production and kit bodyweight, the A1254 no effect TRV is 0.5 mg PCB/kg ww diet for live kit production, and the A1242 TRVs are 1.3 (no effect) to 1.4 mg/kg ww (low effect) for live kit production.

The more conservative TRVs of the ones calculated for mink in this effort–no effect of 0.5 and low effect of 0.6 mg/kg ww diet based on A1254–are recommended for risk assessment purposes to account for the increased toxicity of PCBs that occurs with bioaccumulation and trophic transfer (foodchain transfer from prey to predators), or additive effects of concurrent exposure to co-contaminants that act through the same toxicological mechanisms as PCBs (Section 6.2.1.1).

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[10] The data for live kit production for single-season exposure is supplemented with the results of a single Clophen A50 treatment (12 mg/kg) reported by Kihlström, et al. (1992).

[11] Maternal exposure for 6 months including pregnancy. *In utero* means "in the womb", in other words, before birth.

5.2 Chicken Studies

The results of chicken studies are shown in Figures 17-32. Dose-response relationships are evident for hatchability (Figures 17-24) and chick bodyweight (Figures 25-27). Two dose-response patterns are evident for the effect of A1242 on hatchability (Figure 18)–one based on 3 studies by two research groups [12] (Briggs and Harris 1972; Cecil, et al. 1974; Lillie, et al. 1974, 1975), the other on 1 study by a third research group (Britton and Huston 1973). Each of these response patterns is separately analyzed instead of attempting to choose between the research results. An effect on chick survival is apparent for A1248, but not other Aroclors at the doses tested (Figure 28). There are no consistent dose-response relationships for egg productivity (Figure 29) or egg fertility (Figure 30). Although trends are apparent for chick deformities, studies were not performed at doses sufficiently high to allow interpolation of ED_{25}, except for the field study using field-contaminated feed (Figure 31) (studies based on field contamination are not used for TRV derivation). Only single data points are available for egg concentration and chick survival for each of the Aroclors considered in this effort (Figure 32), so concentration-response relationships cannot be evaluated precluding TRV derivation.

The interpolated TRVs are given in Table 3. The bodyweight-normalized dose TRVs (mg/kg_{BW}-d) are as follows: A1242–0.1-0.5 (no effect) to 0.4-0.8 (low effect) for hatchability, and 0.2 (no effect) to 0.9 (low effect) for chick bodyweight; A1248–0.4 (no effect) to 0.5 (low effect) for hatchability, 0.2 (no effect) to 0.6 (low effect) for chick bodyweight, and 0.2 (no effect) to 0.3 (low effect) for chick survival; and A1254–0.6 (no effect) to 1.2 (low effect) for hatchability.

The interpolated egg TRVs (mg/kg whole egg, ww) are as follows: A1242–1.0 (no effect) to 1.5 (low effect) for hatchability, and 3 (no effect) to 10 (low effect) for chick bodyweight; A1248–0.7 (no effect) to 1.3 (low effect) for hatchability; and A1254–9 (no effect) to 12 (low effect) for hatchability.[13]

Although the lowest TRVs for hen dose are for A1248 and chick survival, little confidence can be placed in the calculated ED_{10} or ED_{25} because the interpolations are performed over a 10-fold dose gradient (Figure 28). Based on the shapes of the better defined dose-response plots for other endpoints, the interpolated values are probably underestimated. A similar concern applies to the no effect TRVs for A1242 or A1248 doses and chick bodyweight (Figure 25). Since two dose-response patterns are evident for A1242 and hatchability (Figure 18), the recommended bird TRVs are based on A1248 and hatchability–0.4 mg/kg_{BW}-d (no effect) and 0.5 mg/kg_{BW}-d (low effect) (bracketed by the two A1242 values).

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[12] Two papers report data from the same experiment (Cecil, et al. 1974 and Lillie, et al. 1974).

[13] Adverse effects have been reported at whole-egg concentrations greater than 4 mg/kg based on the A1254 study by Tumasonis, et al. (1973) in reviews by Barron, et al. (1995) and Hoffman, et al. (1996), which is lower than the egg A1254 TRVs presented here also based in part on Tumasonis, et al. (1973). The difference is that the treatment response used in the present effort is based on the effects occurring during exposure to PCBs (maximal suppression of hatchability at 100 mg/kg in yolk). Tumasonis, et al. (1973) also reported deformities in chicks at yolk concentrations at or above 10-15 mg/kg in the weeks following cessation of exposure to PCBs, which is the basis for the effect levels reported in the reviews. These data were not used in the present effort because the effects occurred after cessation of exposure, and quantitative data on deformity rates were not provided.

For egg TRVs, the best defined concentration-response plots are for A1242 and hatchability (Figure 22) and A1254 and hatchability (Figure 24), in which interpolations are performed within gradients of 2-fold or less. Although the egg TRVs for A1242 chick bodyweight are interpolated over a 7-fold concentration gradient (Figure 27), and combines disparate exposure routes (egg injection and contaminant transfer from exposed hens), the low effect TRV is very close to the treatment mean based on dosed hens and not significantly influenced by the egg injection study (the converse is true for the no effect TRV). The egg TRVs for A1248 and hatchability are interpolated over a 7-fold concentration gradient (Figure 23), and therefore are have greater uncertainty than the A1242 or A1254 TRVs for the same endpoint. The recommended egg TRVs are based on the more sensitive of the Aroclors with well-defined concentration-response plots, that is, A1242 and hatchability–1.0 (no effect) to 1.5 mg/kg ww whole egg (low effect).

6 Uncertainty

Uncertainty is discussed for the method for deriving the TRVs and the application of the TRVs for risk assessment.

6.1 TRV Uncertainty

6.1.1 Confounding Factors

An important potential source of uncertainty is associated with combining the results of separate studies together into aggregated dose-response plots because the studies were not performed under standardized protocols. Differences in results between studies may have occurred that are not linked to treatment doses for several reasons including differences in rearing conditions, feed, animal strains, health or nutritional status, age, exposure routes, or exposure durations. Other possible confounding factors include unsuspected alternate sources of contamination in the feed, water, or experimental facility (either to the same chemical being tested or to another unmeasured chemical), or differences in the composition of the Aroclor batches tested (different lots of the same Aroclor may differ in toxicity due to fluctuations in the composition of toxic PCB congeners or co-contaminants formed during manufacture).

The significance of these potentially confounding factors is assessed by examination of the dose-response plots of the combined studies. Marked deviations from interpretable dose-response patterns indicate that study results are incompatible for some reason. An interpretable dose-response pattern is one that is consistent with known patterns and toxicological theory. The basic pattern is a sigmoid curve in which low doses have minor effects, higher doses exhibit increasingly adverse effects, and the effects at the highest doses asymptotically approach maximum adversity. Two modifications are threshold models, in which increases in dose at low dose levels cause no significant changes in response until a threshold dose is reached, above which the sigmoid pattern applies, and hormetic models, in which doses lower than a threshold for adverse effects show an enhanced (positive) response. Of the endpoints considered in this effort, only two exhibit uninterpretable dose-response patterns–A1254 and egg productivity (Figure 29) or fertility (Figure 30). Either A1254 has no effect on egg productivity or fertility (at the doses tested), or the studies combined into these plots are incompatible for one or more of the factors described above. Regardless of the reason, these endpoints are excluded from the TRV process. Chick survival is also excluded because there are insufficient data to reveal dose-response patterns for any Aroclor (Figure 32). The rest of the endpoints of studies performed with commercial PCB products exhibited interpretable dose-response patterns consistent with one of the models described above, which indicates that the results of the combined studies were not

significantly affected by confounding factors (with the possible exception of A1242 and hatchability discussed below).

6.1.2 Exposure Duration

In addition to the overall screening of interpretable dose-response patterns, it is also possible to specifically assess the possible effects of combining studies with different exposure durations or exposure routes. It is not feasible to exactly match the exposure durations between the studies combined into single plots. Exposure duration ranged from 6 to 14 wk for chicken feeding studies (most between 6 and 9 weeks), and from 3 to 10 months for mink studies performed over a single breeding season. The data are consistent within the range of exposure durations of the combined studies as discussed below.

The studies combined for A1248 and hatchability have similar exposures durations–8 (Lillie, et al. 1975) and 9 wk (Lillie, et al. 1974; Cecil, et al. 1974; Scott 1977)–and exhibit a consistent dose-response pattern (Figure 19). Three studies were combined to evaluate the effect of A1254 on hatchability with exposure durations of 6 (Tumasonis, et al. 1973), 9 (Lillie, et al. 1974 and Cecil, et al. 1974), and 14 wk (Platanow and Reinhart 1973); however, the relative response plots show internally consistent responses (no obvious duration effects) on the basis of either hen dose (Figure 20) or egg concentration (Figure 24). This is partly because the shortest duration treatment (6 wk) was at a high dose that completely suppressed hatchability, but mainly because the results of the 9- and 14-wk studies are remarkably consistent. At first impression, the divergent A1242 and hatchability patterns appear to be related to exposure duration (Figure 18). The pattern showing greater toxicity is largely based on 8- to 9-wk durations (Lillie, et al. 1974, 1975; Cecil, et al. 1974), and the one showing lesser toxicity on 6-wk duration (Britton and Huston 1973), except that the data by Briggs and Harris (1972) with 6-wk exposure is consistent with the pattern exhibited by the 8- to 9-wk exposure studies, and inconsistent with the Britton and Huston study. The divergent A1242 patterns are inexplicable with the available information and therefore are separately assessed. This uncertainty is reflected in the TRV ranges presented for A1242 dose and hatchability.

All of the mink Aroclor feeding studies were performed over single breeding seasons. Three studies are combined for A1242 and live kit production (Figure 2) with rounded exposure durations of 5 (Käkelä, et al. 2001), 8 (Bleavins, et al. 1980) and 10 months (Aulerich and Ringer 1977). No and low effects are bracketed by the hormetic response at 2 mg/kg ww dietary concentration (Aulerich and Ringer 1977) and complete reproductive suppression at 5 mg/kg (Bleavins, et al. 1980) with roughly comparable exposure durations. The treatment at an intermediate dietary concentration (3 mg/kg) has the shortest exposure duration of the combined studies (5 months), which was terminated at the onset of breeding (Käkelä, et al. 2001) in contrast to the other studies, but exhibits a response consistent with the longer duration studies (in fact, plots close to a direct log-linear line between the other studies). Again, there is no evidence that the difference in exposure durations among studies has distorted the concentration-response relationship. Three studies are combined for A1254 and live kit production (Figure 3) with four rounded exposure durations of 3 (Kihiström, et al. 1992), 4 (Aulerich and Ringer 1977), 6 (Wren, et al. 1987), and 10 months (Aulerich and Ringer 1977). Live kit production is almost completely suppressed at all the tested dietary concentrations of 2 mg/kg or greater (3-, 4-, and 10-month exposure durations). An apparent inconsistency occurs at 1 mg/kg, with a 6-month exposure study exhibiting hormesis (Wren, et al. 1987) and a 4-month exposure study showing adverse effects (Aurlerich and Ringer 1977), which are the opposite trends expected based solely on the respective exposure durations (the data are smoothed at this dietary concentration by averaging the two responses). However, since reproduction is unsuccessful at 2 mg/kg (the sole live kit in that treatment soon died),

there is no margin for increasing the A1254 low effect TRV, that is, it must be less than 2 mg/kg ww diet (for a single breeding season). The A1254 TRVs might be overestimated (too high) because they are bracketed at the no-effect side by the results of shorter exposure durations (4 to 6 months), that is, greater adverse effects may occur if mink were exposed to 1 mg/kg for 10 months instead of 4-6 months. The same consideration applies to the low effect TRVs for A1254 and kit bodyweight (Figure 5), which is bracketed by a 10-month exposure study for severe effects and a 6-month exposure study for lesser effects. However, a similar disparity in exposure durations of A1242 studies did not result in an obvious inconsistency in responses.

Two studies are combined for one of the Clophen A50 endpoints (live kits per mated female), with exposure durations of 3 (Kihlström, et al. 1992) and 6 months (Brunström, et al. 2001) (Figure 7). The responses are consistent because the single 3-month exposure treatment was performed at a sufficiently high dose to completely suppress reproduction. Once maximum adversity occurs, there is no scope for further change in response with increased exposure duration.

In contrast to the generally consistent results of combining single breeding season studies of varying exposure durations, exposure duration effects are apparent in both of the studies that included continuous exposures over both 1 breeding season and 2 breeding seasons or 2 generations (Figures 7-10 and 12). The exposure duration was 6 months for the single breeding season treatments in both studies, and was 16 (Restum, et al. 1998) and 18 months (Brunström, et al. 2001) for females continuously exposed over 2 breeding seasons. The second generation females were exposed in the womb (6-month maternal exposure) followed by 12 months postnatal exposure (Restum, et al. 1998). The effect may be more pronounced for live kit production and possibly kit survival compared to kit bodyweight (compare Figures 7 with 9, and 8 or 12 with 10), and appears to be more pronounced for exposure over 2 generations compared to the same adult female continuously exposed over 2 breeding seasons (Figures 8, 10, 12). Since the concentration-response patterns differ for exposures over single versus double breeding seasons or generations, the data are not aggregated.

To summarize, there is no evidence that the range of exposure durations of the studies combined for assessing effects during single breeding seasons resulted in significant inconsistencies in the dose-response patterns for either chicken or mink. The A1254 TRVs for mink might be overestimated (too high) because the effect sizes for live kit production and kit bodyweight are bracketed by shorter exposure duration studies on the no effect side (4 to 6 months) as compared to the severe effect side (10 months), however, a similar disparity for A1242 showed no inconsistencies (a 5-month exposure duration treatment is intermediate in both dietary concentration and response to 8- to 10-month treatments). However, two studies show that the responses to 6-month exposures during a single breeding season differ from the responses to continuous 16- to 18-month exposures over two breeding seasons, and therefore should not be combined into aggregated dose-response plots. Similarly, a study shows that the responses to exposure over a single breeding season should not be aggregated with the responses of females exposed *in utero* followed by 12 months postnatal exposure.

6.1.3 Exposure Route

The same approach can be used to assess the effect of different exposure routes. The exposure route for all of the mink studies was the same, that is, through contaminated diet. For oral dose to chicken, the exposure route was contaminated diet with one exception–contaminated water in the study by Tumasonis, et al. (1973). The data do not show an effect related to this difference in exposure media. The response due to exposure to contaminated water is

consistent with the effect trends of exposure to contaminated diet (Figures 20 and 24). For egg concentration, the exposure route was through hen dietary exposure except for Gould, et al. (1997) in which PCBs were injected into egg yolks. The Gould, et al. study influenced one TRV (A1242 egg residue and chick bodyweight), for which the egg injection data are combined with a single treatment from a hen feeding study (Lillie, et al. 1974, Cecil, et al. 1974) (Figure 27). In addition to the difference in exposure route, the relative "chick" bodyweight for Gould, et al. (1997) is based on 17-d embryos, not on hatched chicks. However, the response trend is reasonably consistent between exposure routes, or, better put, there is no obvious inconsistency between the response of the two studies. In any case, because of the spacing of the treatments, the low effect egg A1242 TRV for chick bodyweight is predominantly influenced by the hen feeding treatment, and the no effect TRV by the egg injection study. This means that the no effect egg TRV for A1242 and chick bodyweight may be less certain in comparison with the low effect TRV.

6.1.4 Linear Interpolation

The appropriate regression technique is a source of uncertainty for the ED_x procedure because the results depend on how well the dose-response relationship is modeled (Section 3). Model uncertainty in the present effort is minimized in three ways. 1) Uncertainties related to characterization of complex dose-response relationships, such as threshold or hormesis models, are avoided by linear interpolation of TRVs between the treatments that bracket the selected effect sizes for no and low effects. It is not necessary to mathematically represent the entire dose-response curve to calculate the ED_{10} or ED_{25}, so long as the overall shape of the dose-response relationship conforms with one of the known patterns. Related to this, extrapolation beyond the empirical data is strictly excluded. 2) The effect sizes (10 % decrease from control for no effect, and 25 % decrease for low effect) are selected to minimize model dependence (Section 3). 3) The results of linear interpolations are only accepted when performed within the steep linear portion of the dose-response plots, and, related to this restriction, confidence in the TRVs interpolated between narrow dose gradients is greater (less uncertainty) than for TRVs interpolated between wider dose gradients. The Aroclor TRVs for mink are interpolated within 2-fold or less gradients in dietary concentration (A1242 or A1254 and live kit production, and the low effect A1254 TRV for kit bodyweight). Most of the bird TRVs are interpolated within 2-fold gradients in dose (A1242 or A1248 and hatchability) or egg concentration (A1242 or A1254 and hatchability), and one of the no effect TRVs for A1242 dose and hatchability is interpolated over a 3-fold gradient. This indicates that uncertainty related to appropriate characterization of the dose-response relationship is low.

Although the TRVs for A1254 dose and hatchability are interpolated over a 4-fold gradient, there is low model uncertainty for the low effect TRV because it coincides with one of the treatment means (Figure 20). However, there is greater model uncertainty for the no effect TRV for A1254 and hatchability because the shape of the dose-response relationship is uncertain over the 4-fold gradient. Similarly, the TRVs for A1242 or A1248 and chick bodyweight (Figure 25), or A1248 and survival (Figure 28) have high model uncertainty because they are interpolated over 10-fold dose gradients (although modeling uncertainty is appreciably less for the low effect TRV for A1242 and hatchability because the treatment mean plots close to the low effect size). Despite the apparent greater sensitivity of chick survival for A1248 (or the no effect TRV for chick bodyweight) compared to hatchability, the A1248 TRVs are based on hatchability because the modeling uncertainty is high for the other endpoints.

To summarize, modeling uncertainty is low for the final TRVs because they are interpolated over narrow dose gradients within well-defined dose-response relationships.

6.1.5 Adjustment of Mink TRVs for Exposure Over 2 Breeding Seasons or 2 Generations

Another source of uncertainty for the mink TRVs concerns the empirical observations that continuous exposure over 2 breeding seasons or 2 generations increases the severity of the reproductive effects of PCBs compared to exposure over a single season, "showing the relevance of long-term exposure for estimation of a LOAEL" (Brunström, et al. 2001). Since the effect has been observed in mink feeding studies both with controlled dosing with one of the European commercial PCB products and with field-contaminated fish from a site in the United States, it is unlikely that it is caused by some unique attribute of the European product or some non-PCB-related contaminant in the field-contaminated fish (also, the field-contaminated fish of the latter study were collected at one time, homogenized, and stored for use throughout the study, so co-contaminant levels did not vary between breeding seasons). This indicates the increased toxicity of PCBs to mink with continuous exposures over multiple breeding seasons or generations may be a general characteristic of PCBs, with implications for long-term occupancy of contaminated sites.

The potential for increased PCB toxicity with extended exposure is relevant for assessing the long-term suitability of habitats for mink because the estimated longevity in the wild is 3 to 6 years, with maximum longevity of 8 to 12 years during which mink are fecund for 7 or more years (Chapman and Feldhamer 1982; Merritt 1987). Unfortunately, mink Aroclor studies have only been performed for single breeding seasons and single generations, so there is uncertainty in either accounting for or ignoring the increase in toxicity associated with exposures over 2 breeding seasons or 2 generations in other studies. If excluded, a habitat remediated on the basis of single-breeding season TRVs may allow for unimpaired mink reproduction during the initial year of occupancy, but not in succeeding years or generations of continued occupancy. The net effect would be that only transient mink would have unimpaired reproduction, but not resident mink that remain in the same locality through multiple years or generations. In other words, the habitat might remain a population sink in which the presence of mink would depend on regular immigration from other areas. If the increase in toxicity related to exposure over multiple years or generations is accounted for by adjusting the single-season TRVs, reproductive impairment by PCBs would not be expected in mink regardless of residence time or number of generations at the site. The uncertainty in this scenario is in determining the appropriate adjustment to Aroclor TRVs when the empirical data are limited to Clophen A50 and field-contaminated fish.

The uncertainty in not making this adjustment would be low if the difference between the effects of exposures to 1 versus 2 breeding seasons or generations was relatively small. However, the study with Clophen A50 showed large decreases in the proportion of females giving birth (57 % decrease in whelping frequency) and the number of live kits per whelped female (47 % decrease) compared to exposures over 1 breeding season (Brunström, et al. 2001), so that only one-fourth of the number of live kits were produced per mated female in the second breeding season compared to the first (Figure 7). The Restum, et al. (1998) study with field-contaminated fish showed similarly large effects for live kit production (Figure 8) and kit survival (Figure 12), as well as a pronounced effect on the bodyweight of kits whelped by 2nd generation females (themselves exposed *in utero* and postnatally) much greater than the effect on kit bodyweight due to exposure to adult female mink over either 1 or 2 breeding seasons (Figure 10).

The weight of evidence indicates that the uncertainty associated with excluding an exposure duration or generational effect may be high, that is, potentially severe adverse effects may be overlooked. However, there is a large range in the ratio of 2-season or 2-generation exposure-based TRVs divided by 1-season exposure TRVs for the various endpoints reported in the two studies, from less than 0.3 to 0.9 (Table 2), which means that selection of an adjustment factor for Aroclor TRVs is correspondingly uncertain. Although the ratios are lowest for live kit production (<0.3-0.4) and kit bodyweight of 2nd generation-exposed females (0.4), the two endpoints used for the mink Aroclor TRVs, the approach taken in this effort is to use the mean ratio of all the endpoints for which low effect TRVs could be calculated (mean of 0.52, n = 7). The mean ratio should have lower uncertainty compared to ratios selected from either end of the range, and is therefore used to adjust the mink Aroclor TRVs in the absence of Aroclor-specific data.

For comparison, the mink TRV for the GLI water quality criteria is based on an A1254 dietary LOEC of 2 mg/kg (Aulerich and Ringer 1977), which was converted to a NOEC of 0.2 mg/kg by dividing by an uncertainty factor of 10 (USEPA 1995a). These values bracket the mink A1254 TRVs derived in this effort. The low effect dietary TRV of 0.6 mg/kg is significantly lower than 2 mg/kg, but, as discussed in Section 3, the LOEC used by the GLI resulted in complete reproductive suppression, therefore the actual lowest dietary concentration associated with the onset of adverse effects is expected to be lower than 2 mg/kg. Since the LOEC resulted in severe effects, the NOEC for the GLI (the sole basis for decision-making in the GLI effort) was conservatively estimated by using a large uncertainty factor, which resulted in a value somewhat lower than the no effect dietary TRV of 0.5 mg/kg based on long-term sustainability. This comparison indicates that an appropriate level of conservatism was used in the GLI effort in estimating a no effect level from less than ideal toxicity data, and that the TRVs derived in this effort are reasonably consistent with the GLI even though the values are adjusted to account for the observed increase in toxicity with continuous exposure over multiple years or generations.

6.1.6. Endpoints and Effect Size

Consistent with the guidance for ecological risk assessment in the Superfund program (USEPA 1997), the toxicological endpoints included in this effort are one that could impact populations–live kit production, kit survival, and kit bodyweight for mink; and hatchability, deformities, chick survival, and chick bodyweight for birds (bodyweight is an indicator of the potential for long-term survival). The main uncertainties with the toxicological endpoints relied on for the TRVs are that data are insufficient for fully evaluating all of the considered endpoints, for example, kit or chick survival might be a more sensitive endpoint than live kit production or hatchability; and data are sparse for other endpoints that could impact populations, such as immune system effects, or neurological or other somatic effects that could impair performance of essential activities such as mating, rearing, hunting, evading predation, migrating, or competing with other species. A possible field example involves Caspian tern exposure to PCBs at Saginaw Bay, MI. Although productivity did not appear to be affected by exposures, elevated plasma PCB level was associated with decreased return of adults to the colonies, suggesting a possible effect on survival (see discussion and references in Hoffman, et al. 1998). The possibility that other endpoints might be more sensitive or result in greater overall impact in the field compared to the endpoints used for TRV derivation in this effort (live kit production, kit bodyweight, and hatchability) is an underlying uncertainty.

The effect sizes used in this effort are chosen for pragmatic reasons–to minimize model dependence, approximate the power of well-designed toxicity studies, and maintain general consistency in approach with other regulatory uses of toxicity test data (Section 4.2). The main uncertainty with the effect size selection is that they are not linked to

population models, that is, the effects of 10 or 25 % decrements in hatchability, live kit production, or kit bodyweight on local populations are not explicitly modeled. There is uncertainty in both directions–a 10 % decrease may result in larger impacts than appropriate for a no effect level, or a 25 % decrease may not result in discernible impacts. As discussed in Section 4.2, this uncertainty is low because of the very steep slope of the dose-response relationship between no effects and severe effects–mostly separated by less than 3-fold gradients in dose or dietary concentration. Since population modeling is irrelevant for either zero impacts or 100 % adverse impacts (the local population will not be impacted by exposures that do not affect individuals, but is clearly not sustainable when reproduction is completely suppressed), modeling could only influence the TRVs within the 2- or 3-fold gradient between the extremes in response.

Such modeling for mink or bird populations would itself have large uncertainty associated with it. There are multiple sources of uncertainty in modeling or measuring population responses to stresses (Lester, et al. 1996; Power, 1997; NRC 1998; Rose 2000; Forbes, et al. 2001; Shea and Mangel 2001; Tyre, et al. 2001). A significant uncertainty in choosing effect sizes based on population models is that "simple, general, *a priori* predictions are not feasible" even with knowledge of life history dynamics and how life history traits are affected by toxicant exposure, because of the large number of factors influencing the outcome (Forbes, et al. 2001). Uncertainty is further increased because exposure to new stressors can change which population traits most influence population growth rates (referred to as "vital rates"). This means that identification of sensitive population traits with prospective demographic studies (prior to exposure to stressors) does not reliably predict which population trait is most important for population impacts following exposure (Cooch, et al. 2001 and references).

> "[T]he vital rate which contributes most to the observed variability in life histories is not necessarily the one to which life histories are most sensitive (which is revealed by the prospective analysis), nor the one that will necessarily make the biggest contribution to variability in another environment. This is especially true in wild populations, where natural selection is likely to minimize variation in those parameters to which population growth (i.e., fitness) is potentially the most sensitive, such that observed variation in growth over time might be reasonably expected to reflect changes in one or more of the parameters to which growth is less sensitive." [citations omitted] (Cooch, et al. 2001).

Exposure to toxic chemicals not only "switches the sensitivity of [population growth rate] to changes in vital rates", but also "increases the sensitivity of organisms to stressors that affect vital rates other than the ones that have been affected by the toxicant" (Kammenga, et al. 2001). An additional uncertainty in identifying sensitive population traits is that the results depend on both the spatial and temporal scales of the assessment (Power 1997; Rose 2000). These considerations mean that there is large uncertainty in applying general population models, and significant uncertainty may be associated even with species- and site-specific models because contaminant exposure may change the interactions between the various population traits and population growth, that is, the pre-exposure demographic model may not apply to post-exposure conditions.

Since the PCB dose-response relationships show a narrow range between the onset of adverse effects and maximum severity, the uncertainty associated with population modeling to refine the choice of effect size for determining TRVs is considered excessive relative to the constrained range over which the TRVs can vary.

6.2 Application Uncertainty

There are several sources of uncertainty associated with the application of the TRVs to field situations. In addition to the usual uncertainties of extrapolating from laboratory studies to field conditions, and, in the case of the bird TRVs, extrapolating between species, there are additional uncertainties associated with measuring PCBs as Aroclors in environmental samples, or measuring or estimating TEQ, and their use in risk assessments.

6.2.1 PCBs and Risk Assessment

Polychlorinated biphenyls (PCBs) are not a single chemical, but are mixtures of large numbers of different chemicals based on a common structure–a biphenyl "frame" with variable numbers of chlorine atoms attached to it. Each different arrangement of the number of chlorine atoms and their spatial position on the biphenyl is a separate PCB chemical, referred to as a "congener". There are 209 possible PCB congeners, each with slightly to very different chemical, physical, and toxicological properties. The complex mix of congeners with differing properties presents several challenges for assessing the risks of PCB exposures.

First, the toxicity of PCBs is caused by a subset of the congeners. The best understood subset is the dioxin-like congeners that act wholly or in part through the same mechanism as dioxin (Van den Berg, et al. 1998). The dioxin-like congeners, often referred to as "planar" or "coplanar" congeners, are capable of binding with the same cellular protein–aryl hydrocarbon receptor (AhR)–that binds with dioxin in the initial step of a cascade of interactions leading to expression of toxic effects. However, some of the non-coplanar, non-dioxin-like PCB congeners or their metabolites also have toxic effects through separate toxic mechanisms that are not as well understood (Fisher, et al. 1998). Some of the coplanar congeners may act through multiple pathways, that is, they may contribute to both dioxin-like and non-dioxin-like toxicity. The combined toxicity of the dioxin-like congeners can be estimated through a toxic equivalent (TEQ) approach (described below), but, at present, there is no comparable approach for estimating the combined effect of non-dioxin-like congeners.

Second, each of the different commercial PCB products are comprised of different proportions of congeners, which means that the toxicity varies for the different Aroclors, for example, A1242 is more toxic than A1260 because A1242 has a higher proportion of dioxin-like congeners. The uncertainty related to differences in congener composition between Aroclors is addressed in this effort by separately assessing the toxicity of each Aroclor. The toxicity of a European product (Clophen) is assessed separately from American products (Aroclors) for the same reason.

Third, once released into the environment, the differences in the chemical and physical properties of the congeners result in differences in their fate and transport, that is, in their persistence, how they move through the environment, and in which components they are likely to accumulate in greater concentrations. For example, the lower chlorinated congeners (ones with few chlorine atoms) volatilize (evaporate), solubilize (partition to water), and degrade more readily so they tend to decrease over time, while the heavier, more chlorinated congeners are less volatile, less soluble, often less readily degraded, and therefore are more persistent in the environment. Conversely, under anaerobic conditions (without free oxygen), some of the higher chlorinated congeners may be more readily degraded than lower chlorinated ones. Therefore, congener composition of PCBs in the environment can change over time, a process described as "weathering". The congener composition may also be altered as PCBs are passed through foodchains, that is, the congener pattern retained in animals may differ from the pattern in their food. The changes in congener proportions mean that the toxicity of PCBs in the environment differs from the toxicity of the source Aroclors depending on the type and degree of weathering and bioaccumulation.

6.2.1.1 Aroclor-based Risk Assessment

The original toxicity testing of PCBs was performed with commercial Aroclors, with the results presented in terms of Aroclor dose or concentration. An advantage of the Aroclor approach is that studies show the combined effects of all the toxicological modes of actions of the various congeners (both dioxin-like and non-dioxin-like) and manufacturing impurities, and their net interactions (additive, synergistic, and antagonistic). This means that, for exposures to tested commercial PCB products that have not been significantly weathered, there is little uncertainty related to multiple toxic mechanisms or interactions among congeners or other co-contaminants formed in the PCB manufacturing process. Also, there is a large ecotoxicological database for Aroclor effects.

The main uncertainties of Aroclor-based risk assessment are related to the changes in congener composition following release to the environment (weathering and bioaccumulation), which can affect measurements of PCB levels and estimations of risk. Various methods have been used to determine the amount of PCBs in a sample as a concentration of an Aroclor or a mix of Aroclors (summarized in Eisler and Belisle 1996). Uncertainty is introduced because the congener composition of environmental samples may differ from that of any particular Aroclor or combinations of Aroclors, which results in larger variability in analytical results between laboratories than is usual for other chemical analyses. In formal terms, measurement error is larger for Aroclor analyses compared to congener-specific analyses.

Changes in congener patterns also can affect toxicity. Loss of lower chlorinated congeners to volatilization or degradation can increase the proportional dioxin-like toxicity of the remaining PCBs because many of the dioxin-like congeners are persistent. Anaerobic degradation may reduce toxicity due to higher chlorinated dioxin-like congeners, although the products may also be toxic (e.g., Ganey, et al. 2000). Foodchain transfers may increase the toxicity of the PCBs retained in organisms (see references in Lugwig, et al. 1996). For example, the biomagnification factors (BMF) for dioxin-like congeners are twice as high as the BMFs for total PCBs in zooplankton or *Mysis* (a freshwater invertebrate) feeding on phytoplankton, or *Diporeia* (another invertebrate) feeding on *Mysis* (Trowbridge and Swackhamer 2002). This preferential biomagnification increases the toxicity of the PCBs in the organism relative to the source PCBs because of the increased proportion of dioxin-like congeners accumulated in their tissues. Since the organisms in this example are representative of the base of an aquatic foodchain, the altered pattern with increased toxicity will be passed to animals feeding on zooplankton or aquatic invertebrates. This is evident in one study of animals that feed on plankton, the sediment-to-biota BMF for bioassayed TEQ was 10 times greater than the BMF for PCBs (Jones, et al. 1993). There is inconsistent evidence for preferential biomagnification of dioxin-like congeners by piscivorous (fish-eating) fish (Jones, et al. 1993; Metcalfe and Metcalfe 1997), but marked preferential biomagnification of dioxin-like congeners has been reported in some studies of piscivorous birds (gulls and cormorants) and mammals (otters) (Koslowski, et al. 1994; Guruge and Tanabe 1997; Leonards, et al. 1997). In general, risk assessments based on the original source Aroclor are likely to underestimate the risk of bioaccumulated PCBs (Ludwig, et al. 1996; Giesy and Kannan 1998).

Another potential source of uncertainty in Aroclor-based assessments is that total risk in the field may be underestimated because the approach does not readily allow for combined assessment of the effects of PCBs and additional contaminants with the same toxicological mode of action. For example, contributions to dioxin-like toxicity may be made by dioxins, polychlorinated dibenzofurans, and other chemicals in addition to PCBs. The source of the additional chemicals may be from the same facility that released PCBs or from separate sources (either local or distant through atmospheric transport). Regardless of the sources, the presence of additional

chemicals with dioxin-like activity in the field reduces the amount of PCB exposure that can be tolerated by wildlife in comparison to controlled exposures to commercial PCB products in captive animals not simultaneously exposed to additional dioxin-like chemicals.

6.2.1.2 Dioxin Toxic Equivalent-based Risk Assessment

Another approach for assessing the risks of PCBs is based on the total dioxin-like effects (TEQ), either calculated from congener-specific analytical data or measured by *in vitro* bioassays. Some advantages of these approaches are that they are not subject to the analytical uncertainties related to the potential mismatches between Aroclor standards and weathered PCBs, they facilitate assessment of the combined toxicity of dioxin-like PCB congeners and other dioxin-like contaminants, and TRVs can be based on studies of any chemical with dioxin-like toxicity when the results are given as TEQ (in contrast to Aroclor-specific results, which can not be generalized to other dioxin-like chemicals).

The main uncertainties associated with the currently available TEQ approaches for risk assessments are related to the methods used to determine the TEQ, and the potential significance of non-dioxin-like effects.

One TEQ approach is based on congener-specific analytical data in which the concentration of each dioxin-like congener is multiplied by its toxic equivalency factor (TEF), the fractional toxicity of that congener compared to 2,3,7,8-TCDD, which are summed for all dioxin-like congeners to give the toxic equivalent concentration (TEQ). By this approach, TEQ represents the concentration of the most toxic dioxin congener that is expected to equal the potency of the mix of PCB congeners in the sample. The approach permits inclusion of additional chemicals with dioxin-like potency such as polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans.

An obvious source of uncertainty are the TEF values. The current consensus TEFs are "order of magnitude estimates of the toxicity of a compound relative to TCDD" based on a tiered evaluation of the relative potencies (REPs) reported in a variety of studies (Van den Berg 1998). The order of magnitude estimate is an "illustration of the overall uncertainty in TEF values based on the differences in outcomes of the different end points and the variation in available data for the different congeners" (van Leeuwen 1999). Another indication of TEF uncertainty is the difference in TEF schemes by different groups and at different times, which also limits the usability and comparability of TEQ studies unless the full congener data were reported so that results can be converted to a common basis (Dyke and Stratford 2002). Another source of uncertainty is the additivity assumption in the TEQ calculation. Although dose additivity is supported by many studies (Van den Berg 1998), non-additive interactions also are reported. These uncertainties are believed to be less than the level of uncertainty associated with Aroclor-based assessments, supported by examples of good correlations in practice between TEQs and toxic effects (Van den Berg 1998; van Leeuwen 1999; Birnbaum 1999; Tillitt 1999), however, caution has also been expressed for the use of the TEF approach for PCBs based on "nonadditive interactions, coupled with the unusually broad range of TEF values observed for some PCB congeners" (Safe 1998). An uncertainty related to analytical issues is that most of the dioxin-like PCB congeners occur in very low concentrations, which means that measurement errors of congeners with high TEF values will be magnified in TEQ calculations. An extreme example in a recent study is unuseable analytical data for congener 126 due to interference (Trowbridge and Swackhamer 2002). Since congener 126 is often one of the greatest contributors to the TEQ of PCBs, the calculated TEQs of this study are

underestimated and inappropriate for risk assessment purposes.[14] Since the TEFs for different dioxin-like congeners vary by several orders of magnitude, small measurement errors for highly potent congeners can result in large errors in TEQ calculations. Another uncertainty is that TEFs are not presently available for all chemicals with potential dioxin-like activity, although TEFs are available for the ones shown to account for the majority of the dioxin-like toxicity in intact animals.

Another approach for determining TEQs is by *in vitro* bioassays, in which the response of cultured cell lines exposed to dioxin-like chemicals is measured. An advantage of the bioassay approach is that it provides an integrated measure of the effects of all the chemicals in a mixture that affect dioxin-like responses with all of their interactions (additive, synergistic, and antagonistic). Interactions can occur between dioxin-like chemicals or with non-dioxin-like chemicals that modulate dioxin-like responses. The main uncertainties are related to interspecific differences in cell responses, and issues involved in extrapolation of effects in isolated cells to intact animals. Cells of different species show differences in interactive effects between PCB congeners. For example, at high doses, PCB congener 52, one of the di-*ortho*-substituted congeners [15], inhibits cellular responses to dioxin or dioxin-like PCB congeners in bioassays performed with mouse and rat cell lines, but not with guinea pig or human cell lines (Aarts, et al. 1995). This means that the presence of di-*ortho*-substituted congeners in Aroclors may reduce the TEQ measured in bioassays performed with cultured mouse or rat cell lines (reportedly by as much as 2 orders of magnitude in comparison with a calculated TEQ that assumes additivity, see references in Aarts, et al. 1995), but not in bioassays performed with cultured guinea pig or human cell lines. In addition to measurement uncertainties related to interspecific differences in cellular responses, there are uncertainties related to extrapolation of *in vitro* responses of isolated cell cultures to *in vivo* [16] responses of intact animals. One of the advantages of bioassays–an integrated response to direct administration of complex environmental mixtures to cells–also introduces uncertainty because the dosing does not reflect the pharmacokinetics [17] in intact animals. Although many chemicals are capable of binding with the Ah receptor, their ability to cause dioxin-like toxicity also depends on their pharmacokinetic behavior, for example, how rapidly they are metabolized (degraded) (Bimbaum 1999) or distribution patterns within an animal (for examples of species differences in PCB distribution among organs see Bachour, et al. 1998). *In vitro* bioassays may therefore show responses to chemicals that have little or no effect in intact animals.

> "In summary, a single *in vitro* assay based on a single surrogate species may not accurately predict the toxicity of a chemical or complex mixture following exposure to other species.

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[14] The purpose of this particular study was to investigate the transfer of PCB congeners through selected trophic levels in an aquatic ecosystem, for which the loss of data for a single dioxin-like congener is not crucial. However, a similar data gap would be unacceptable for a risk assessment.

[15] Di-*ortho*-substituted congeners have 2 chlorine atoms attached in the positions closest to the bond that holds the biphenyl "frame" together, with variable numbers of chlorines attached at other positions. The 2 *ortho* chlorines prevent these congeners from taking on the planar configuration necessary for activating the Ah receptor, and therefore they do not exhibit dioxin-like toxicity, but, at high concentrations, inhibit the Ah receptor (with varying efficiency in different species) so that it becomes less responsive to dioxin-like congeners.

[16] *In vivo* means "in the living", and refers to experiments performed with intact living organisms.

[17] Pharmacokinetics refer to the rates of various processes that affect the movement and form of chemicals in living organisms including uptake, distribution, binding, biotransformation, and elimination.

> Nevertheless, the use of *in vitro* assays provides a general tool as a prescreening method of TEQs in environmental samples. However, it does not replace *in vivo* experiments when determining TEFs for dioxinlike compounds." (Van den Berg, et al. 1998).

Another source of uncertainty for TEQ-based risk assessments is that the current approach does not include non-dioxin-like toxicity (by definition). Non-dioxin-like toxicity, that is, toxic effects not mediated by the Ah receptor, may be induced by non-coplanar PCB congeners (Fisher, et al. 1998), or biotransformed PCB products such as hydroxylated metabolites (Schuur, et al. 1998) or methylsulfonyl metabolites (Johansson, et al. 1998). The uncertainty would be low if the thresholds for non-dioxin-like effects are lower than for dioxin-like effects, in which case assessments based on dioxin-like effects would be protective for all adverse effects. A comparison of the available data on non-AhR-mediated neurotoxicity [18] and dioxin-like effects in wildlife indicated that the dioxin-like effects are more sensitive endpoints (Giesy and Kannan 1998). Although encouraging, the comparison is provisional because the neurotoxic effects are not as well studied as dioxin-like effects, non-dioxin-like effects include endpoints other than neural effects, and some endpoints may be affected through both AhR-mediated and non-dioxin-like pathways. For example, thyroid function may be affected by both pathways. In one study, the relative potency of different extracts in depressing serum levels of thyroxine (the main thyroid hormone) in rats was not well predicted by TEQ. An air extract proportionally enriched in lower chlorinated congeners and depleted in higher chlorinated congeners, dioxins, and dibenzofurans, exhibited more severe effects on thyroxine levels at the same TEQ concentrations as soil or dust extracts with the converse congener compositions (Figure 2A in Li and Hansen 1996). Although in most situations, TEQ-based assessments show good correlations with toxic effects and appear to provide an adequate margin of safety for non-dioxin-like effects as well, the potential for non-dioxin-like processes remains an uncertainty until our understanding of non-AhR-mediated processes improves.

> "The spectrum of activity produced by [non-coplanar] congeners has not been fully explored, and the mechanisms by which their known actions are produced are emerging but remain to be fully elucidated. The toxicodynamic interactions between non-coplanar PCBs and the actions produced by coplanar PCBs which bind to the Ah-receptor remain to be investigated. Similarly, the actions and interactions of hydroxylated and other metabolites of PCBs remain to be studied in sufficient depth. At the present time, it is clear that non-coplanar PCBs alter signal transduction pathways and interrupt intracellular Ca^{2+} homeostasis. A common site of action responsible for all of the actions of non-coplanar PCBs, analogous to the Ah-receptor utilized by coplanar PCBs, has not been found ..." (Fisher, et al. 1998).

In summary, the two major approaches for PCB risk assessment have converse strengths and uncertainties. For Aroclor-based approaches, uncertainties are low for interactions between congeners and multiple toxic mechanisms, but uncertainties increase as the congener composition of environmental samples is altered from the original Aroclor composition by weathering or bioaccumulation. The Aroclor approach does not readily allow for assessment of combined risk of PCBs and other chemicals with dioxin-like toxicity. For the currently available TEQ-based approaches, results are not affected by weathering, but uncertainties are associated with TEF values and additivity assumptions for calculated TEQs, interspecific differences in cellular responses and *in vitro* to *in vivo* extrapolations for bioassay TEQs, and an inability to account for non-dioxin-like effects. The TEQ approaches

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[18] The situation is complicated by possible neurotoxicity caused by dioxin-like congeners as well as non-dioxin-like congeners.

facilitate assessment of combined risk of PCBs and other chemicals with dioxin-like toxicity, although uncertainty remains for calculated TEQs by the limited number of consensus TEFs (risks may be underestimated due to dioxin-like chemicals without TEFs), and for bioassay TEQs by toxicokinetic considerations (risks may be overestimated by cellular responses to chemicals that would not cause toxicity in intact animals).

6.2.2 Interspecific Extrapolation and Laboratory-to-Field Extrapolation

Extrapolation of toxicity data from tested species to wildlife is another source of uncertainty in TRVs that includes two categories–extrapolations between different species, and extrapolations from laboratory conditions (captivity) to field conditions.[19] There is no interspecific extrapolation for mink because the TRVs are based on studies of captive mink, but the difference between conditions in captivity and in the wild is a source of uncertainty. Both categories of uncertainty pertain to the bird TRVs, which are based on studies of captive chicken.

Captive animals are well fed, do not have to compete for resources, are less active, usually protected from weather extremes, and in general are subject to less stress compared to wild animals.[20] The toxicity of a tested chemical is often greater in stressed animals, for example, in a review of fish toxicity, nutritional status altered the relative toxicity between laboratory and field situations by as much as 10-fold, and temperature stress by as much as 100-fold (Heugens, et al. 2001). Stressor interactions are often nonlinear, complicating their assessment (Power 1997), and may involve complex interactions. The adverse effects of PCBs on stress responses were increased by poor nutritional status (Quabius, et al. 2000), which implies that a synergistic interaction of PCB exposure and nutritional stress could decrease the capability to respond to additional stressors. Kammenga, et al. (2001) discuss examples in which exposure to toxic substances increases sensitivity to other environmental variables such that the exposed population becomes more vulnerable to changes in these other variables than to the direct toxicant effects. Another difference between captive and wild animals is that wild animals are exposed to a wider variety of toxic chemicals. In addition to interactions between stresses due to chemicals with different toxicological actions, wild animals may be exposed to chemicals that act though the same toxicological mechanisms as the chemical of concern, thereby increasing the toxicity of a given level of exposure compared to captive animals with controlled exposures. Other endpoints might be more sensitive or result in greater overall impact in the field compared to the endpoints studied under controlled conditions (Section 6.1.6). Related to this, laboratory studies are usually not performed over an entire life cycle, and effects in the field may differ from those in laboratory studies because of cumulative effects, greater sensitivity at other developmental or life stages than the ones investigated, or interactions between generations (for example, impaired parental care).

An example of greater adverse effects in a field study than expected from laboratory studies on related species is the high sensitivity of wood ducks to egg TEQ concentrations in the field–significant reductions in hatchability and live duckling production occurred at egg TEQs of 20-50 ppt (White and Seginak 1994; White and Hoffman 1995),

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[19] Another source of uncertainty for risk assessment involves the exposure assumptions. This is not addressed here because it does not affect the TRV values. For example, risk in the field may differ from modeled risk because the wildlife are feeding on a different mix of food items or in other locations than assumed in the model that results in differences between field and modeled exposures. However, exposure uncertainty concerns whether the TRVs have been or are likely to be exceeded, not the particular values of the TRVs.

[20] This may not hold for species that can not tolerate captivity, that is, the stress of being confined may outweigh the reduced stress of being cared for, but species intolerant of captivity can not be used for toxicity testing.

which are comparable to the sensitivity of chicken–onset of embryonic mortality and deformities at 10-20 ppt dioxin egg concentration (Verrett 1976 as cited in Hoffman, et al. 1996), and LD_{50} (lethal dose to 50 % of embryos) of 122-297 ppt (Henshel, et al. 1997). This outcome would not be expected on the basis of laboratory studies with other ducks, which show much less sensitivity to PCBs compared to chicken–LD_{50} of 3-40 ppb congener 77 (one of the dioxin-like congeners) in chicken eggs, but no effects in mallard or goldeneye duck eggs at 5000 ppb congener 77 (various studies, see Table 3 in Hoffman, et al. 1996); and reduced hatchability at less than 1 ppm A1242 in chicken eggs, but no effects on hatchability at 105 ppm A1242 in mallard eggs (various studies, see Table 2 in Hoffman, et al. 1996). Based on these laboratory comparisons, ducks are at least 100 times less sensitive than chicken to PCBs and dioxin-like effects. The unexpected sensitivity of wood ducks in the field may have occurred because of differences among duck species (wood duck may be orders of magnitude more sensitive than mallard or goldeneye), unmeasured co-contaminant exposure contributing to toxicity in the field, stressor interactions not present in captivity, or exposure duration effects. Another example involves adverse effects on terns in the Great Lakes (see discussion in Hoffman, et al. 1998).

The sensitivity of different bird species to PCBs spans several orders of magnitude, and chicken are the most sensitive of the species tested to date (Bosveld and Van den Berg 1994; Barron, et al. 1995; Eisler and Belisle 1996; Hoffman, et al. 1996 and 1998). Use of chicken-based TRVs is inappropriate when species-specific toxicity data are available, and is generally considered inappropriate when data are available for closely related species (although the available toxicity data for ducks poorly predicted field effects for wood duck). The chicken-based PCB TRVs are recommended as a conservative estimator of risk for birds of unknown sensitivity to PCBs. Since chicken are more sensitive than other bird species tested so far, the likelihood of chicken TRVs under predicting risk for other species of unknown sensitivity is probably low, therefore use of uncertainty factors for interspecific extrapolation is not recommended. Although the same rationale indicates that chicken data for PCB toxicity is likely to overestimate risks to PCBs for other bird species, the wood duck example shows that this is not certain–the margin between laboratory effect levels in chicken and field effect levels in other species may be unexpectedly small. Also, PCB or dioxin toxicity has been studied in a relatively small number of bird species under controlled conditions. While the extremes of sensitivity are known to widely diverge, the overall distribution of species sensitivities within this range is poorly known.

The degree of conservatism of applying unmodified chicken-based PCB TRVs to species of unknown sensitivity can be evaluated by comparison to the bird PCB TRV used in the Great Lakes Initiative (GLI) for deriving water quality criteria for the protection of wildlife (USEPA 1995a). The GLI PCB TRV for birds is based on a LOAEL of 1.8 mg/kg_{BW}-d in pheasant (Dahlgren, et al. 1972), which was divided by an interspecific extrapolation uncertainty factor of 3 and a LOAEL to NOAEL uncertainty factor of 3. Therefore the calculated LOAEL for species of unknown sensitivity was 0.6 mg/kg_{BW}-d and the NOAEL 0.2 mg/kg_{BW}-d (only the NOAEL was used for deriving the water quality criteria). These values bracket the recommended TRVs of 0.4 to 0.5 mg/kg_{BW}-d based on chicken PCB TRVs without uncertainty factors. This comparison demonstrates that the conservatism of chicken-based PCB TRVs is consistent with that of previous agency practice for determining environmental PCB limits for protection of wildlife.

In summary, the bird TRVs proposed in this effort provide an appropriate level of conservatism for estimating risk to species of unknown sensitivity to PCBs. The TRVs are unlikely to underestimate risk. By design, they are more likely to overestimate risk, which is a necessary bias for accounting for the uncertainty regarding the sensitivity of untested species. Although interspecific differences in PCB sensitivity span several orders of magnitude, indicating

potentially large uncertainty in assessing risk to untested species, the degree of conservatism associated with the TRVs in the present effort is consistent with prior agency practice.

There is no interspecific extrapolation for the mink TRVs, but uncertainty is associated with laboratory to field extrapolation. The uncertainty of laboratory to field extrapolations is that potential effects are more likely to be underestimated, rather than overestimated, for the various reasons discussed above. For Aroclor-based risk estimates in particular, a common observation is that toxicity is underestimated. This may be due to preferential biomagnification of toxic congeners that increase toxicity compared to the source Aroclor; exposure to other contaminants that either act through the same toxicological mechanisms as PCBs, thereby decreasing the amount of PCB exposure that can be tolerated without adverse effects, or acting as separate but additional stressors; or other non-chemical stressor interactions. These sources of uncertainty are addressed by the recommendation to use the lower of the derived TRVs.

As discussed in Section 6.1.5, the recommended mink TRVs are reasonably consistent with the value used by the GLI for calculating water quality criteria for protection of wildlife.

7. Conclusions

This effort demonstrates that toxicity reference values (TRVs) can be successfully derived through evaluation of dose-response plots in which data are aggregated from multiple studies by normalizing the treatment responses by the respective control responses of each study. The combined data sets better define the shape of dose-response relationship by increasing the number of doses plotted, thereby providing more information for decision-making compared to statistically-defined no or lowest observed adverse effect levels (NOAELs or LOAELs), which are influenced by multiple factors unrelated to toxicity and do not provide dose-response information. Although uncertainties may be introduced by differences in the experimental protocols of the various studies that are combined, such as differences in exposure duration or route, significant effects are readily apparent as inconsistencies in the dose-response plots.

The results of this exercise show that dose-response plots are not highly sensitive to moderate differences in exposure duration. The few differences in exposure route among the aggregated studies also did not result in obvious distortions of dose-response relationships (contaminated food vs. contaminated water, or egg injection vs. maternal transfer to eggs). In the cases in which dose-response inconsistencies are apparent between study results, the data can be stratified (considered separately) for analysis if multiple patterns are evident, or that endpoint can be dropped from further consideration if the data exhibit no interpretable pattern. In other words, the dose-response plots provide their own safeguard against utilization of incompatible data by exhibiting divergent patterns or uninterpretable relationships inconsistent with known toxicological models.

The dose-response plots exhibit very steep transitions between PCB exposures causing no adverse effects and those resulting in severe adversity–mostly less than 2- or 3-fold gradients in dose or dietary concentration between the response extremes. This has two implications: 1) small exceedances of PCB TRVs are likely to result in severe effects on reproductive success, and 2) the calculated PCB TRVs are relatively insensitive to the choice of effect size (the percent decrease in response that is of concern for risk management) because the range of values over which the TRVs can vary is narrow.

Two significant observations can be made from the dose-response plots for mink (actually dietary concentration-response plots). 1) PCBs exhibit a hormetic effect (enhanced reproductive performance) at doses lower than the threshold for adverse effects for the number of live kits produced per mated female in feeding trials performed with either commercial PCB products or field-contaminated prey. 2) In both commercial PCB product (Clophen A50) and field-contaminated prey studies with mink, the exposure-response relationships differ between studies performed over a single breeding season versus those in which exposures are continued over 2 breeding seasons or 2 generations of female mink. Continuous PCB exposure over 2 breeding seasons or 2 generations of female mink results in more severe adverse effects on live kit production, kit survival, and, to a lesser extent, kit bodyweight, in comparison to the effects of exposure over a single breeding season. The mean difference in low effect TRVs for the various endpoints in the two studies is a 50 % decrease associated with 2-breeding season or generation exposures as compared to single-breeding season exposure. This has obvious implications for long-term sustainability of mink at contaminated sites. Since 2-breeding season or generation studies have not been performed with Aroclors, the mink Aroclor TRVs are adjusted by the mean response decrement observed in the Clophen and field-contaminated studies to ensure long-term sustainability.

TRVs based on controlled exposures to Aroclors are given in Table 1 (Section 1). The lower of the TRVs are recommended to account for increases in toxicity PCBs in the field compared to that of Aroclors under controlled conditions, which may be related to changes in source congener composition by weathering and bioaccumulation, concurrent exposure to other contaminants acting through the same toxicological mechanisms as PCBs (thereby reducing the tolerable exposure to PCBs), or interactions with other stressors (chemical, physical, or biological) not present in captivity. Uncertainty factors are not recommended for interspecific extrapolation because the TRVs are based on data for sensitive species.

Although the TRVs are conservatively derived (chicken are sensitive to PCBs, and mink values are adjusted for long-term exposures), the recommended values and level of conservatism are consistent with prior agency practice. Both the bird and mink TRVs are bracketed by the NOAEL and LOAEL values used in the development of PCB water quality criteria for the protection of wildlife by the Great Lakes Initiative. As such, the recommended TRVs represent a refinement of the toxicity information used for the GLI, and share a similar degree of conservatism in their application.

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Figure 1. Live Kits per Mated Female Mink Exposed to Commercial PCB Product for 1 Breeding Season

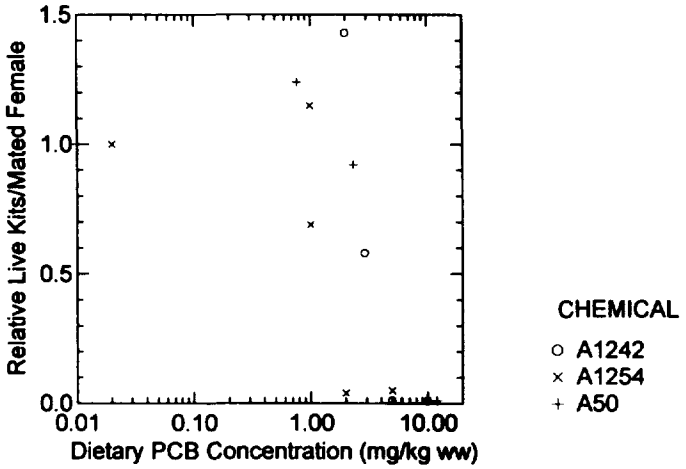
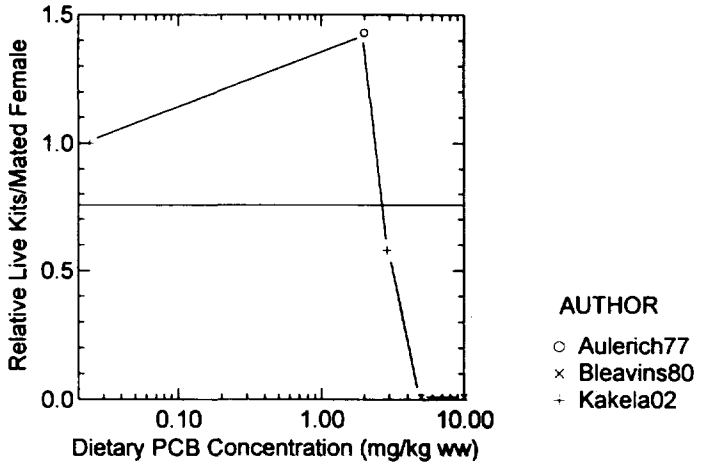


Figure 2. Live Kits per Mated Female Mink Exposed to Commercial Aroclor 1242 for 1 Breeding Season



Author is lead author and date. See notes to Table 3 for citations

Figure 3. Live Kits per Mated Female Mink Exposed to Commercial Aroclor 1254 for 1 Breeding Season

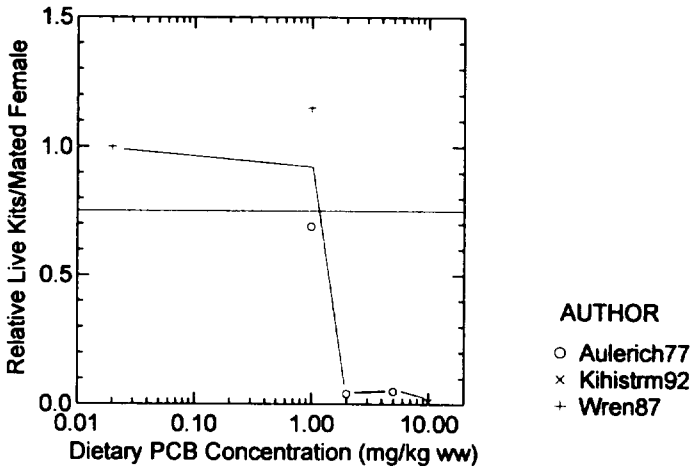


Figure 4. Mink Kit Bodyweight, Maternal Exposure to Commercial PCB Product for 1 Breeding Season

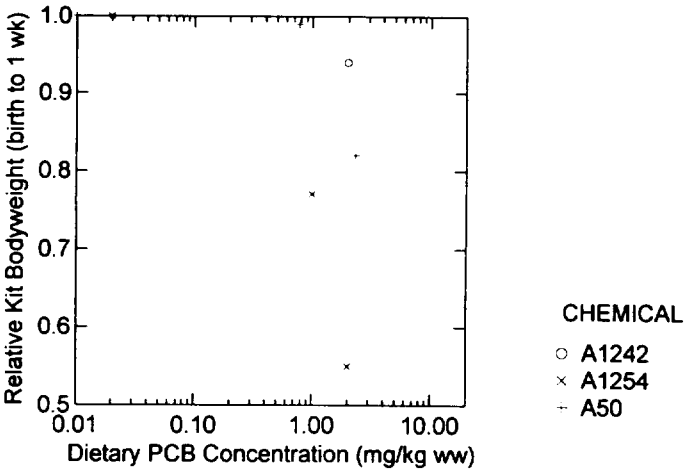


Figure 5. Mink Kit Bodyweight at Birth, Maternal Exposure to Commercial Aroclor 1254 for 1 Breeding Season

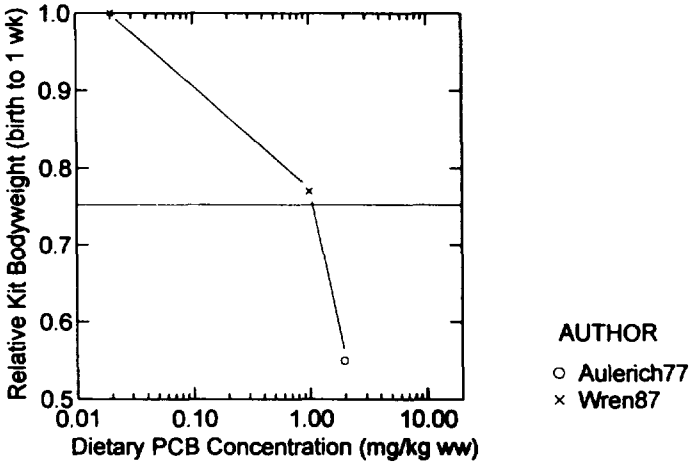


Figure 6. Mink Kit Survival, Maternal Exposure to Commercial Aroclor 1254 for 1 Breeding Season

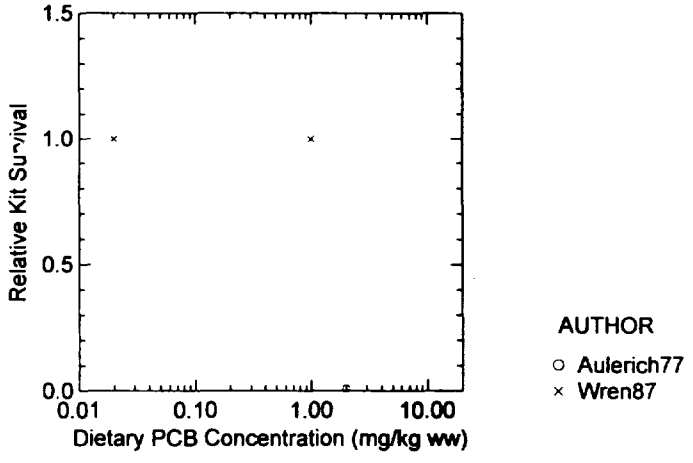


Figure 7. Live Kits per Mated Female Mink Exposed to Commercial Clophen A50 for Multiple Breeding Seasons (Brunström, et al. 2001; Kihlström, et al. 1992)

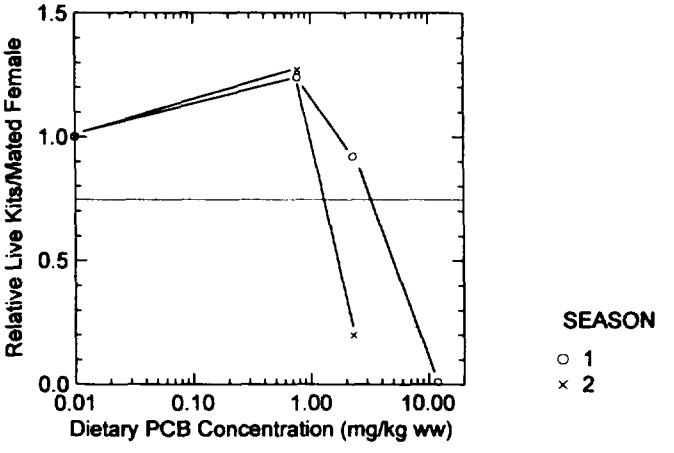


Figure 8. Live Kits per Mated Female Mink Exposed to Field-contaminated Fish for Multiple Breeding Seasons or Generations (Restum, et al. 1998)

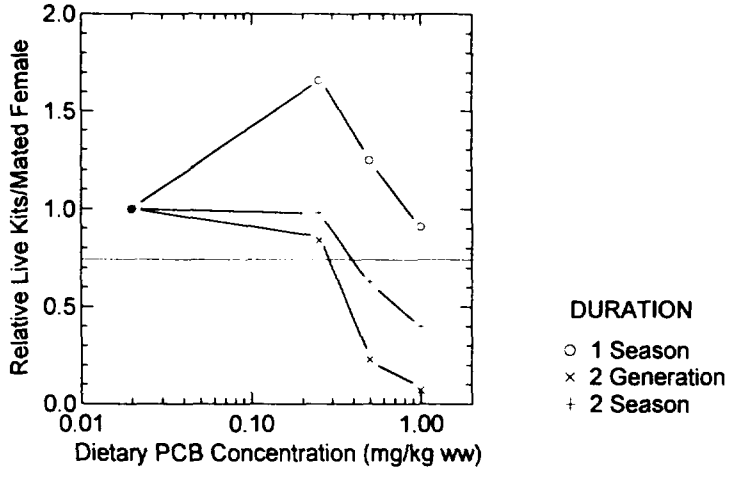


Figure 9. Mink Kit Bodyweight at Birth, Maternal Exposure to Commercial Clophen A50 for Multiple Breeding Seasons (Brunström, et al. 2001)

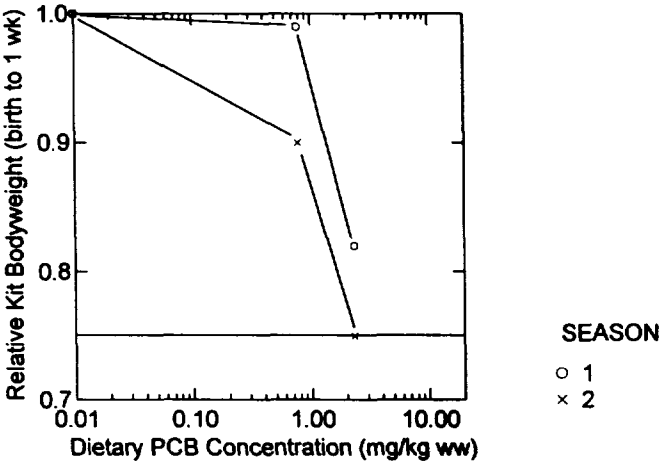


Figure 10. Mink Kit Bodyweight at Birth, Maternal Exposure to Field-contaminated Fish for Multiple Breeding Seasons or Generations (Restum, et al. 1998)

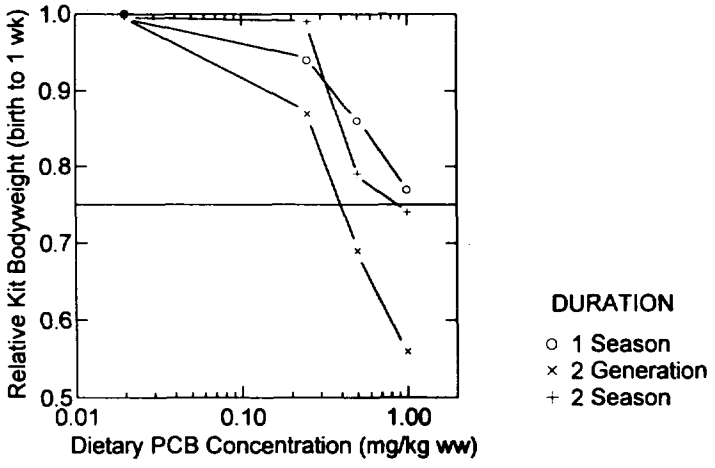


Figure 11. Mink Kit Survival, Maternal Exposure to Commercial Clophen A50 for 2 Breeding Seasons (Brunström, et al. 2001)

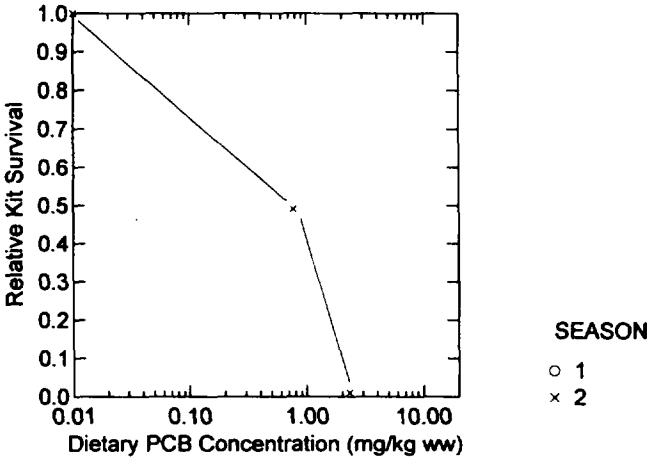


Figure 12. Mink Kit Survival, Maternal Exposure to Field-contaminated Fish for Multiple Breeding Seasons or Generations (Restum, et al. 1998)

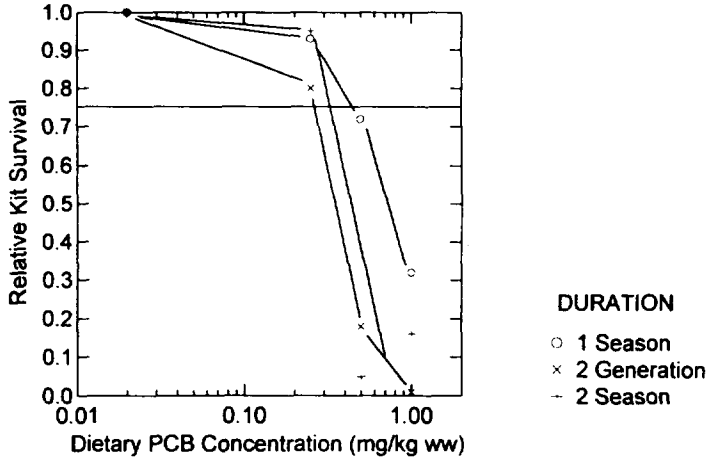


Figure 13. Live Kits per Mated Female Mink Exposed to Field-contaminated Prey for 1 Breeding Season

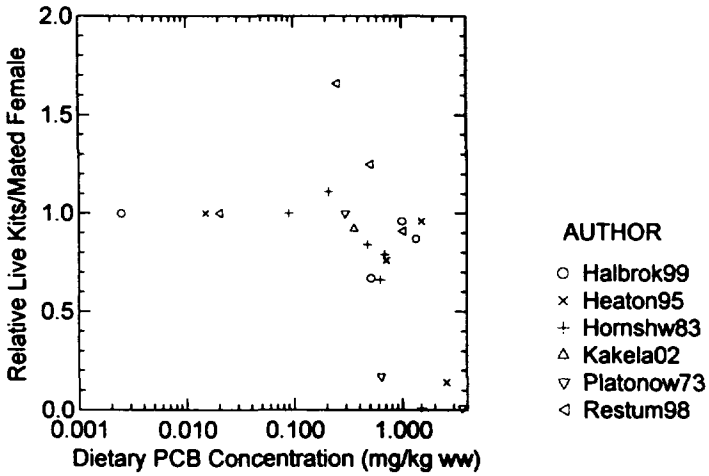


Figure 14. Mink Kit Bodyweight, Maternal Exposure to Field-contaminated Fish for 1 Breeding Season

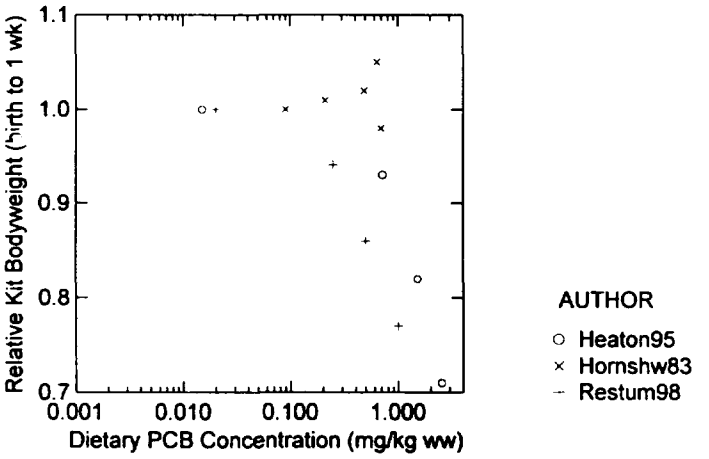


Figure 15. Mink Kit Survival, Maternal Exposure to Field-contaminated Prey for 1 Breeding Season

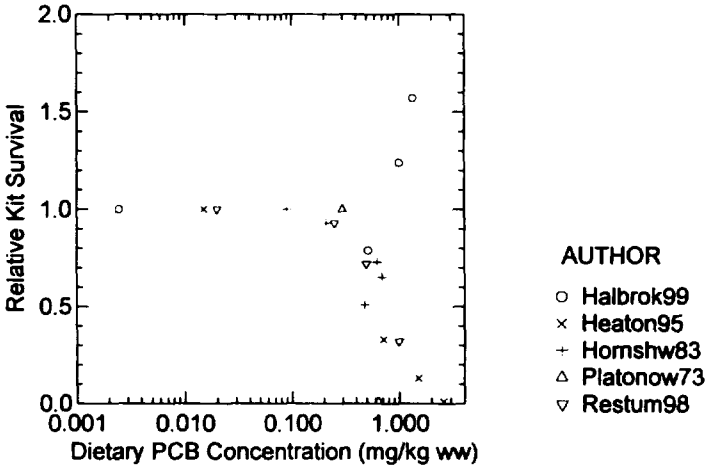


Figure 16. Comparison of Dose-response Relationships for Individual and Aggregated Studies of Hatchability vs. A1248 Dose to Hens

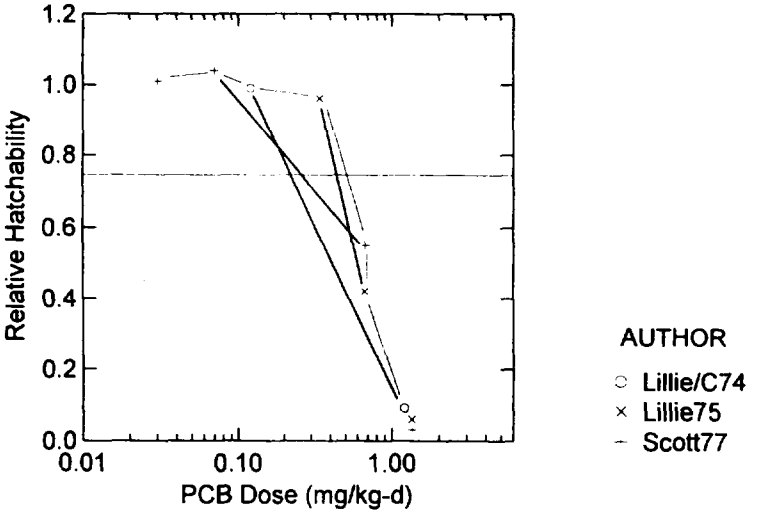


Figure 17. Hatchability, PCB Dose to Chicken Hens

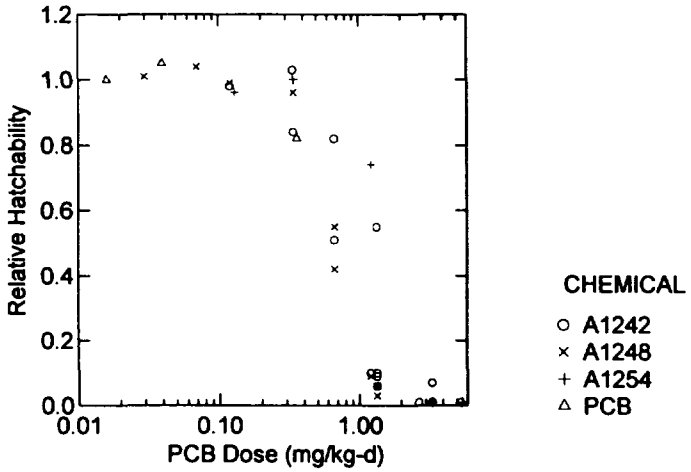
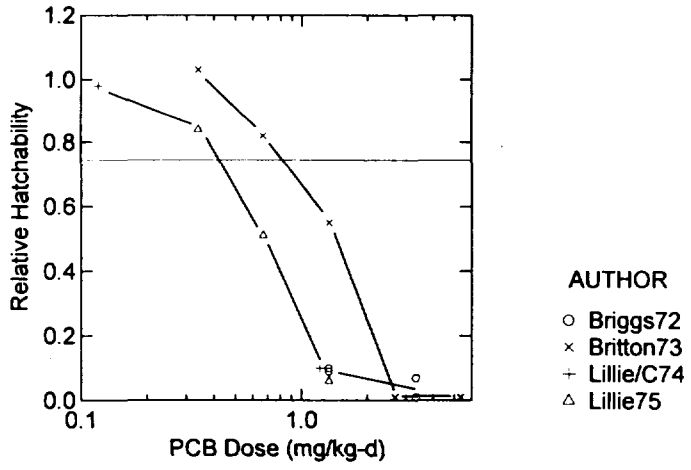


Figure 18. Hatchability, Aroclor1242 Dose to Chicken Hens



Author is lead author and date. See notes to Table 3 for citations.

Figure 19. Hatchability, Aroclor 1248 Dose to Chicken Hens

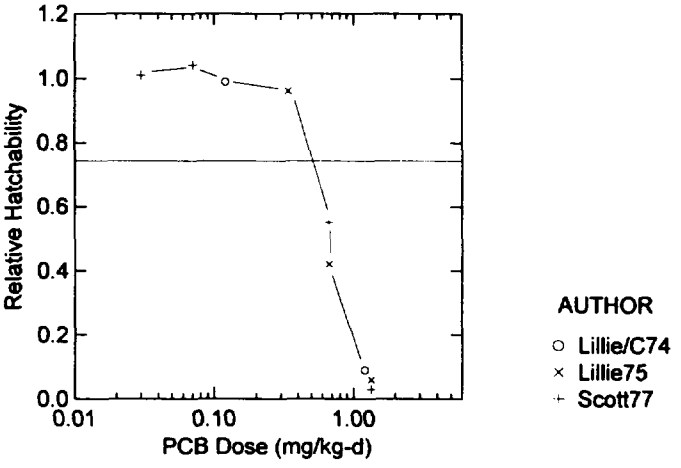


Figure 20. Hatchability, Aroclor 1254 Dose to Chicken Hens

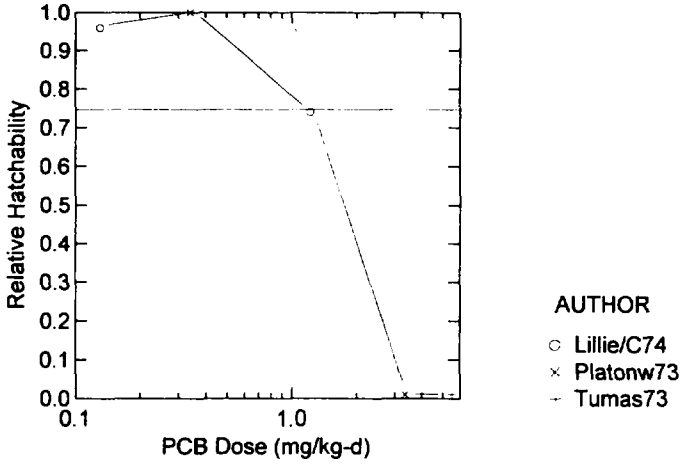


Figure 21. Hatchability, PCB Residues in Chicken Eggs

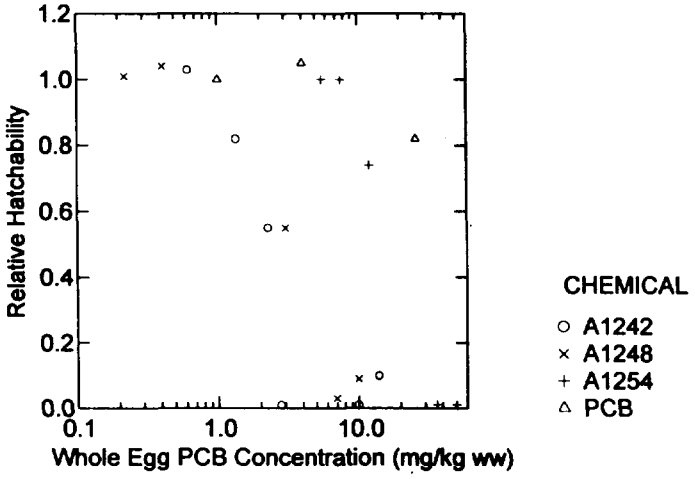


Figure 22. Hatchability, Aroclor 1242 Residues in Chicken Eggs

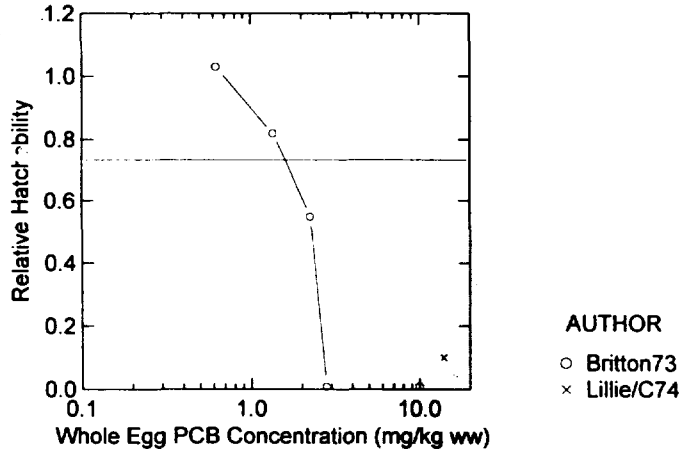


Figure 23. Hatchability, Aroclor 1248 Residues in Chicken Eggs

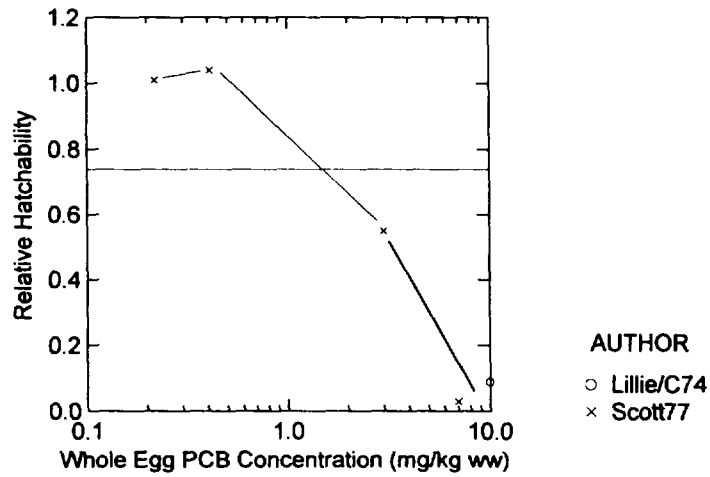


Figure 24. Hatchability, Aroclor 1254 Residues in Chicken Eggs

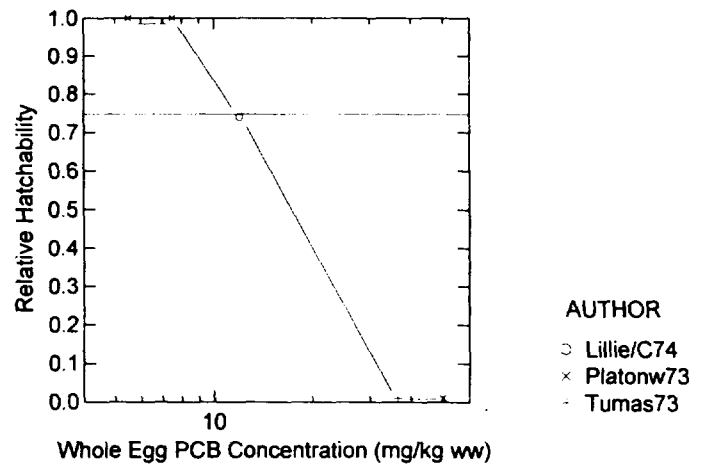


Figure 25. Chick Bodyweight, PCB Dose to Chicken Hens

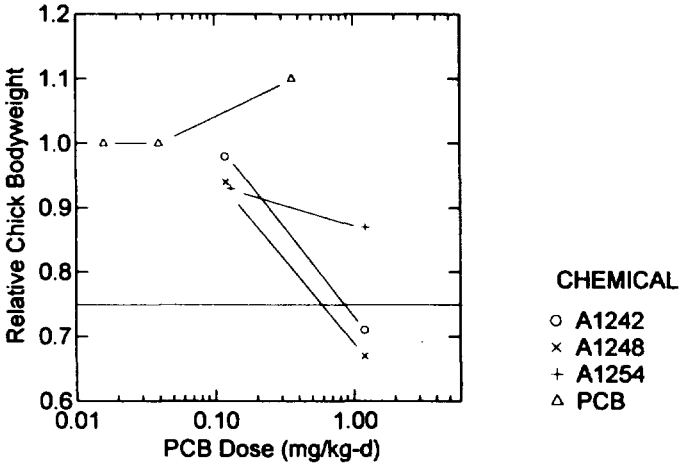


Figure 26. Chick Bodyweight, PCB Residues in Chicken Eggs

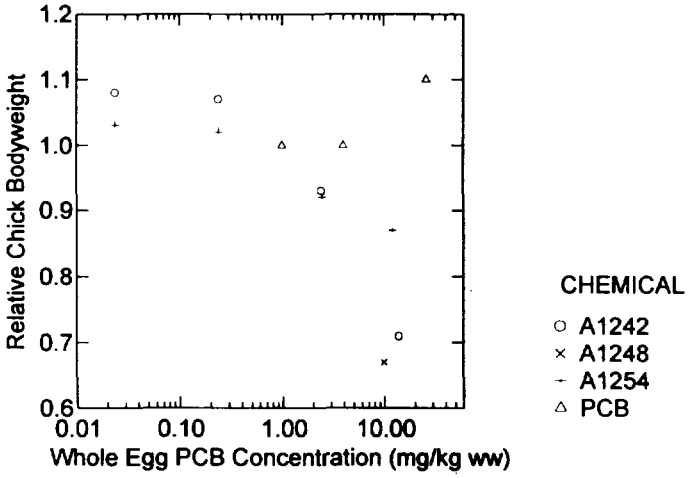


Figure 27. Chick Bodyweight, Aroclor 1242 Residues in Eggs

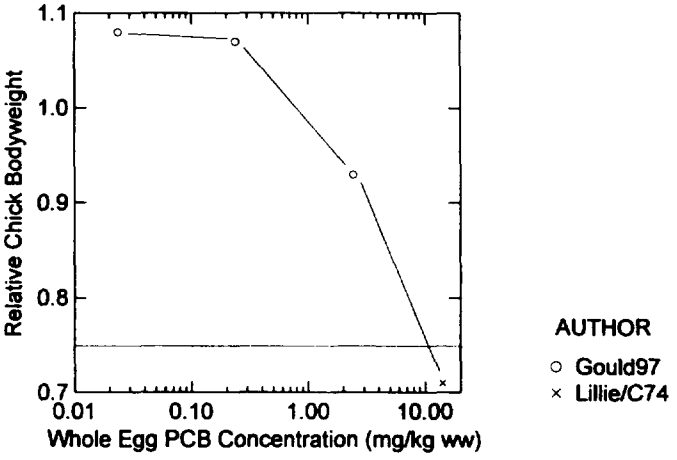


Figure 28. Chick Survival, PCB Dose to Chicken Hens

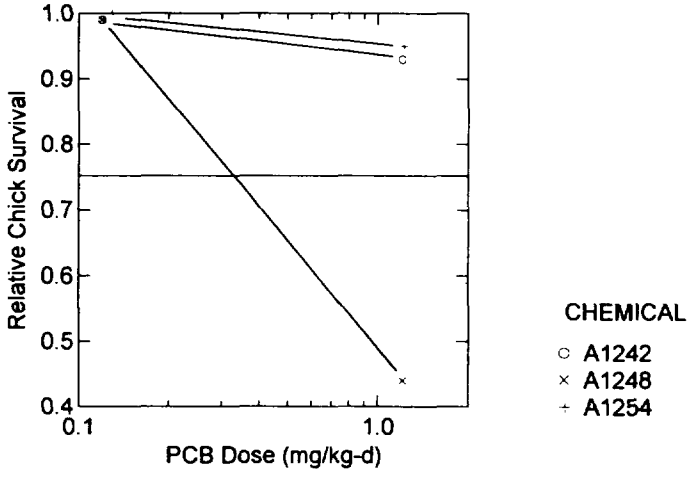


Figure 29. Egg Productivity, PCB Dose to Chicken Hens

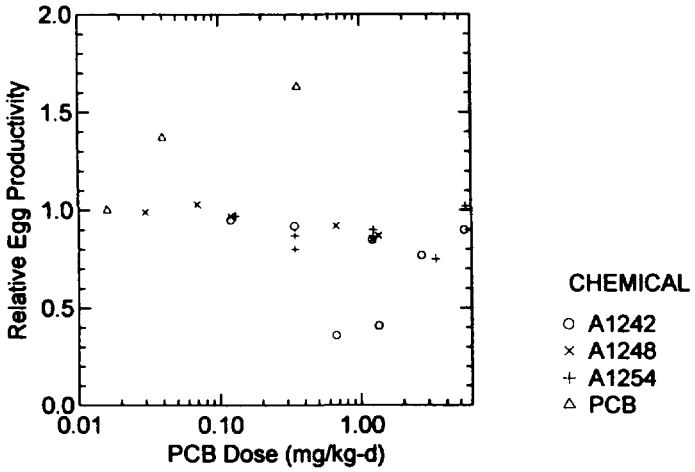


Figure 30. Egg Fertility, PCB Dose to Chicken Hens

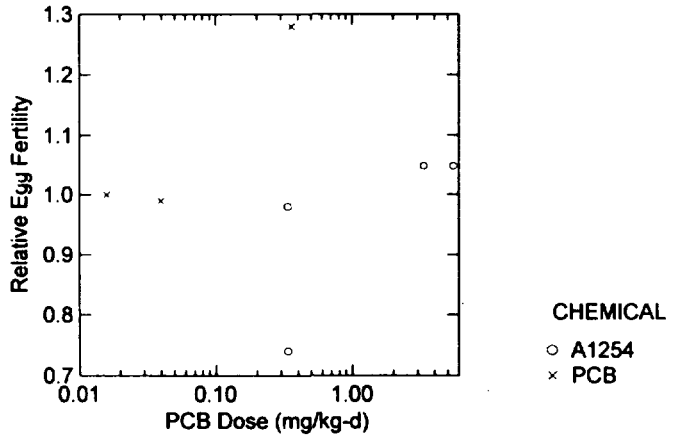


Figure 31. Chick Deformity, PCB Dose to Chicken Hens

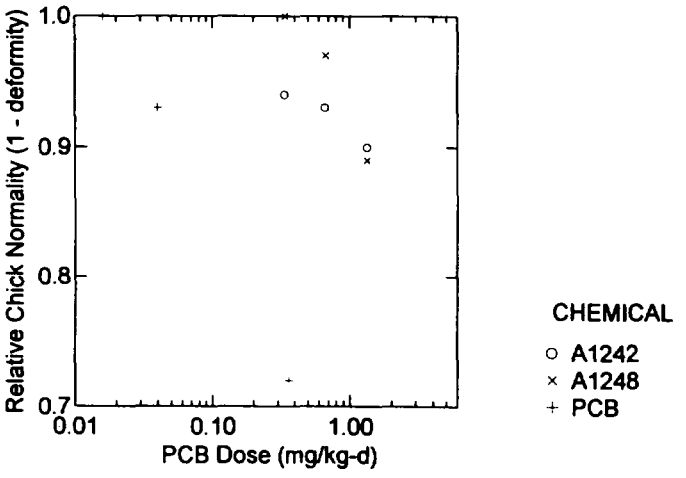


Figure 32. Chick Survival, PCB Residues in Chicken Eggs

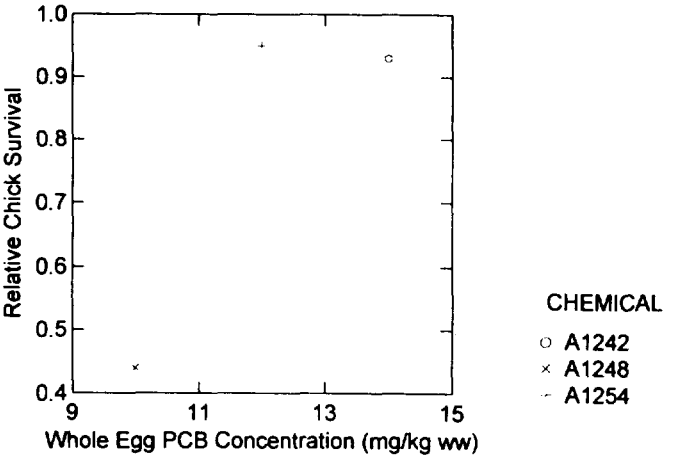


Table 2. Log-Linear Interpolation of PCB Toxicity Reference Values (TRV) for Mink

Chemical or Field study author	Response	Exposure Duration	Control RR	Treatment conc < TRV conc	RR	Treatment conc > TRV conc	RR	Target RR	P	TRV	Effect level	Study
			M_i	C_j	M_j	C_{j+1}	M_{j+1}					
Aroclor feeding studies												
A1242	live kit/ mated ♀	1 season	1	2	1.43	2.88	0.58	0.75		2.68	low effect	Aulerich77, Kakela02
			1	2	1.43	2.88	0.58	0.9		2.51	no effect	Aulerich77, Kakela02
A1254	live kit/ mated ♀	1 season	1	1	0.92	2	0.04	0.75		1.14	low effect	Wren87, Aulerich77
			1	1	0.92	2	0.04	0.9		1.02	no effect	Wren87, Aulerich77
A1254	kit bodywt	1 season	1	1	0.77	2	0.55	0.75		1.07	low effect	Wren87, Aulerich77
			1	0.02	1			0.9		>0.02	no effect	Wren87
A1254	kit survival	1 season	1	0.02	1	2	0	0.75		<1.00	low effect	Wren87, Aulerich77
			1	0.02	1			0.9		>0.02	no effect	Wren87
Comparison of 1 breeding season exposure vs 2 breeding seasons or generations continuous exposure												
A50	live kit/ mated ♀	1 season	1	2.31	0.92	12	0	0.75		3.13	low effect	Brunstm01, Kihistm92
		1 season	1	2.31	0.92	12	0	0.9		2.39	no effect	Brunstm01, Kihistm92
		2 season	1	0.77	1.27	2.31	0.2	0.75		1.31	low effect	Brunstm01
		2 season	1	0.77	1.27	2.31	0.2	0.9		1.13	no effect	Brunstm01
Ratio 2 season / 1 season			*0.47 no effect*									
Ratio 2 season / 1 season			*0.42 low effect*									
Restum	live kit/ mated ♀	1 season	1	1	0.91			0.75		>1.00	low effect	Restum98
		2 season	1	0.25	0.98	0.5	0.63	0.75		0.39	low effect	Restum98
		2 generation	1	0.25	0.84	0.5	0.23	0.75		0.28	low effect	Restum98
Ratio 2 season / 1 season			*<0.39 low effect*									
Ratio 2 generation / 1 season			*<0.28 low effect*									
Restum	kit bodywt	1 season	1	1	0.77			0.75		1.00	low effect	Restum98
		2 season	1	0.5	0.79	1	0.74	0.75		0.87	low effect	Restum98
		2 generation	1	0.25	0.87	0.5	0.69	0.75		0.40	low effect	Restum98
Ratio 2 season / 1 season			*0.87 low effect*									
Ratio 2 generation / 1 season			*0.40 low effect*									
Restum	kit survival	1 season	1	0.25	0.93	0.5	0.72	0.75		0.45	low effect	Restum98
		2 season	1	0.25	0.95	0.75	0.11	0.75		0.32	low effect	Restum98
		2 generation	1	0.25	0.8	0.5	0.18	0.75		0.26	low effect	Restum98
Ratio 2 season / 1 season			*0.72 low effect*									
Ratio 2 generation / 1 season			*0.58 low effect*									
Mean ratio 2 season or gen/ 1 season			*0.52 low effect*			(all studies)						

Notes for Table 2.

bodywt - bodyweight
conc - dietary concentration of PCBs (mg/kg wet weight (ww))
RR - relative response = treatment response / control response
Kit bodyweight is for birth to 1 week age.
TRV - toxicity reference value for dietary PCBs (mg/kg wet weight (ww))

$$\text{Log}_{10}\,TRV = \text{Log}_{10}\,C_j + (((M_i * P) - M_j) * ((\text{Log}_{10}\,C_{j+1} - \text{Log}_{10}\,C_j) / (M_{j+1} - M_j)))$$

$$TRV = 10^{\text{Log}_{10}\,TRV}$$

Study - lead author, date; see notes for Table 4 for citations

A1254 live kit/mated 1 season M_j of 0.92 is the mean of 1.15 (Wren87) and 0.69 (Aulerich77) both at 1 mg/kg dietary concentration.
Restum kit survival 2 season M_j of 0.11 at C_j of 0.75 are the means of 0.05 and 0.16 (M_j) at 0.5 and 1.0 (C_j), respectively.

Table 3. Log-Linear Interpolation of PCB Toxicity Reference Values (TRV) for Chicken

Chemical	Response	Control RR M_1	Treatment dose < TRV dose D_j	RR M_j	Treatment dose > TRV dose D_{j+1}	RR M_{j+1}	Target RR P	TRV	Effect level	Study
Hen Dose (mg/kg$_{BW}$-d)										
A1242	hatchability	1	0.67	0.82	1.34	0.55	0.75	0.80	low effect	Britton73
A1242	hatchability	1	0.34	1.03	0.67	0.82	0.9	0.52	no effect	Britton73
A1242	hatchability	1	0.34	0.84	0.67	0.51	0.75	0.41	low effect	Lillie75
A1242	hatchability	1	0.12	0.98	0.34	0.84	0.9	0.13	no effect	Lillie/Cecil74
A1242	chick bw	1	0.12	0.98	1.21	0.71	0.75	0.86	low effect	Lillie/Cecil74
A1242	chick bw	1	0.12	0.98	1.21	0.71	0.9	0.24	no effect	Lillie/Cecil74
A1248	hatchability	1	0.34	0.96	0.67	0.55	0.75	0.48	low effect	Lillie75; Scott77
A1248	hatchability	1	0.34	0.96	0.67	0.55	0.9	0.38	no effect	Lillie75; Scott77
A1248	chick bw	1	0.12	0.94	1.21	0.67	0.75	0.61	low effect	Lillie/Cecil74
A1248	chick bw	1	0.12	0.94	1.21	0.67	0.9	0.17	no effect	Lillie/Cecil74
A1248	survival	1	0.12	0.99	1.21	0.44	0.75	0.33	low effect	Lillie/Cecil74
A1248	survival	1	0.12	0.99	1.21	0.44	0.9	0.18	no effect	Lillie/Cecil74
A1254	hatchability	1	0.34	1	1.22	0.74	0.75	1.16	low effect	Platonw73; Lillie/Cecil74
A1254	hatchability	1	0.34	1	1.22	0.74	0.9	0.56	no effect	Platonw73; Lillie/Cecil74
Egg Concentration (mg/kg, ww)			conc		conc					
		M_1	C_j	M_j	C_{j+1}	M_{j+1}	P	TRV	Effect level	Study
A1242	hatchability	1	1.35	0.82	2.26	0.55	0.75	1.54	low effect	Britton73
A1242	hatchability	1	0.62	1.03	1.35	0.82	0.9	1.00	no effect	Britton73
A1242	chick bw	1	2.44	0.93	14	0.71	0.75	10.19	low effect	Gould97; Lillie/Cecil74
A1242	chick bw	1	2.44	0.93	14	0.71	0.9	3.10	no effect	Gould97; Lillie/Cecil74
A1248	hatchability	1	0.41	1.04	3	0.55	0.75	1.33	low effect	Scott77
A1248	hatchability	1	0.41	1.04	3	0.55	0.9	0.72	no effect	Scott77
A1254	hatchability	1	7.5	1	12	0.74	0.75	11.79	low effect	Platonw73; Lillie/Cecil74
A1254	hatchability	1	7.5	1	12	0.74	0.9	8.99	no effect	Platonw73; Lillie/Cecil74

Notes for Table 3.

bw - bodyweight
conc - whole egg PCB concentration, mg/kg, ww
dose - bodyweight-normalized ingestion, mg PCB/kg$_{BW}$-d
RR - relative response = treatment response / control response
Study - lead author, date; see notes for Table 5 for citations
TRV - toxicity reference value for PCB dose (D) (mg/kg$_{BW}$-d) or whole egg concentration (C) (mg/kg wet weight (ww))

$$\text{Log}_{10}\,TRV = \text{Log}_{10}\,D_j + (((M_1 * P) - M_j) * ((\text{Log}_{10}\,D_{j+1} - \text{Log}_{10}\,D_j) / (M_{j+1} - M_j)))$$

$$\text{Log}_{10}\,TRV = \text{Log}_{10}\,C_j + (((M_1 * P) - M_j) * ((\text{Log}_{10}\,C_{j+1} - \text{Log}_{10}\,C_j) / (M_{j+1} - M_j)))$$

$$TRV = 10^{\text{Log10 TRV}}$$

Table 4. Mink PCB Toxicity Studies

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
1	reported as A1254, from cow	5.2 month	0.64 mg/kg (control 0.3 mg/kg)	1.23 mg/kg liver (control 0.39 mg/kg); 0.97 mg/kg muscle (control 0.23 mg/kg)				0.17		0, 1 d
		3.4 month	3.6 mg/kg	11.99 mg/kg liver; 3.31 mg/kg muscle	0	0	0	0		
2	A1242 product	9.7 month	2 mg/kg (control NA)		1	1.37	1.43	1.43	0.94 birth	1.42 4 wk
	A1254 product	4.2 month	1 mg/kg (control NA)		0.8	0.90	0.86	0.69		
		9.7 month	2 mg/kg (control NA)		0.29	0.24	0.14	0.04	0.55 birth	0 4 wk
		4.2 month	5 mg/kg (control NA)		0.25	0.50	0.20	0.05		
3	NA (PCB type not identified)	2.2 month	3.3 mg/kg + 3.3 mg/kg DDT (control 0.05 mg/kg)	86 mg/kg fat (control 14 mg/kg)	0.79	0.57	0.20	0.17	0.72 birth	0.21 5 d

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			11 mg/kg	280 mg/kg fat	0	0	0	0		
4	A1242 product	8.1 month	5 mg/kg (control NA)		0	0	0	0		
			10 mg/kg		0	0	0	0		
5	reported as A1254, Green Bay alewife	7 month	0.21 mg/kg (control 0.09 mg/kg)	8.1 mg/kg adipose (control 2.9 mg/kg)	0.92	1.15	1.26	1.11	1.01 birth 1.02 4 wk	0.93 4 wk
	L Michigan Whitefish	7 month	0.48 mg/kg	13 mg/kg adipose	0.89	0.91	0.95	0.84	1.02 birth 0.88 4 wk	0.51 4 wk
	Saginaw Bay sucker	7 month	0.63 mg/kg	10 mg/kg adipose	1.00	0.80	0.67	0.66	1.05 birth 0.91 4 wk	0.73 4 wk
	L Erie perch	7 month	0.69 mg/kg	13 mg/kg adipose	0.91	0.93	0.88	0.79	0.98 birth 0.80 4 wk	0.65 4 wk
	Saginaw Bay carp	7 month	1.5 mg/kg	37 mg/kg adipose	0.30	0.56	0	0		
	Erie perch & Saginaw wht sucker	7 month	0.66 mg/kg (control 0.04 mg/kg)		0.58	0.37	0.19	0.11	0.86 birth	0 4 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
6	A1254 product	6.1 month	1 mg/kg (control 0.02 mg/kg)	2.8 mg/kg liver (control 0.09 mg/kg)	0.99	1.09	1.16	1.15	0.77 1 wk 0.75 3 wk, 0.71 5 wk	1.00 5 wk nearly all starvation (control 75 % trauma or infection, but no starvation)
7	Clophen A50	3 month	12 mg/kg	181 mg/kg fat 4.0 mg/kg muscle	0.11	0.12	0	0		
	A1254	3 month	10 mg/kg	74 mg/kg fat 1.3 mg/kg muscle	0.34	0.66	0	0		
8	PCB - sum of 1242, 1248, 1254, and 1260; TEQ - H4IIE bioassay; Saginaw carp	6 month	PCB 0.72 mg/kg (control 0.015 mg/kg); TEQ 19.4 pg/g (control 1 pg/g)	PCB 2.2 mg/kg liver (control 0.1 mg/kg) TEQ 495 pg/g (control <10 pg/g)	1.00	0.93	0.76	0.76	0.93 birth; 0.67 3 wk; 0.79 6 wk	0.33 6 wk
			PCB 1.53 mg/kg TEQ 40 pg/g	PCB 3.1 mg/kg liver TEQ 439 pg/g	1.00	1.02	0.96	0.96	0.82 birth; 0.67 3 wk 0.41 6 wk	0.13 6 wk
			PCB 2.56 mg/kg TEQ 80.8 pg/g	PCB 6.3 mg/kg liver TEQ 656 pg/g	1.00	0.58	0.14	0.14	0.71 birth	0 3 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
9	PCB - sum of 1242, 1248, 1254, and 1260; TEQ - H4IIE bioassay; Saginaw carp	6 month (P_1 1992)	PCB 0.25 mg/kg (control 0.02 mg/kg) TEQ 7.1 pg/g (control 1 pg/g)		1.36	1.16	1.19	1.66	0.93-0.94 birth 0.75-0.89 3 wk 0.75-0.85 6 wk	 1.06 3 wk 0.93 6 wk
			PCB 0.5 mg/kg TEQ 13.6 pg/g		1.35	1.02	0.91	1.25	0.84-0.87 birth 0.67-0.75 3 wk 0.65-0.68 6 wk	 0.81 3 wk 0.72 6 wk
			PCB 1.0 mg/kg TEQ 26.4 pg/g		1.16	1.02	0.77	0.91	0.75-0.79 birth 0.51-0.59 3 wk 0.35-0.49 6 wk	 0.32 3 wk 0.32 6 wk
		16 month (P_1 1993)	PCB 0.25 mg/kg TEQ 7.1 pg/g	PCB 0.98 mg/kg liver (control 0.07 mg/kg)	1.02	0.95	0.96	0.98	0.88-1.09 birth 0.87-0.91 3 wk 0.92 6 wk	 0.99 3 wk 0.95 6 wk
			PCB 0.5 mg/kg TEQ 13.6 pg/g	PCB 0.89 mg/kg liver	0.78	0.92	0.80	0.63	0.77-0.81 birth 0.65-0.67 3 wk 0.93 6wk	 0.62 3 wk 0.05 6 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			PCB 1.0 mg/kg TEQ 26.4 pg/g	PCB 1.57 mg/kg liver	0.66	0.63	0.59	0.40	0.73-0.74 birth 0.50-0.59 3 wk 0.60-0.66 6 wk	 0.15 3 wk 0.16 6 wk
		12 month F_1 of 6-month exposed parents (F_1-1 1993)	PCB 0.25 mg/kg TEQ 7.1 pg/g	PCB 0.63 mg/kg liver (control 0.02 mg/kg)	0.85	1.05	0.96	0.84	0.87 birth 1.03-1.10 3 wk 0.89-0.95 6 wk	 0.76 3 wk 0.80 6 wk
			PCB 0.5 mg/kg TEQ 13.6 pg/g	PCB 0.96 mg/kg liver	0.76	0.88	0.31	0.23	0.64-0.73 birth 0.42 3 wk 0.54 6 wk	 0.16 3 wk 0.18 6 wk
			PCB 1.0 mg/kg TEQ 26.4 pg/g	1.47	0.63	0.53	0.09	0.07	0.51-0.60 birth	0 3 wk
10	reported as A1260 Poplar Creek & Clinch River fish	7 month	0.52 mg/kg (control <0.005 mg/kg)	<0.005 mg/kg liver (control <0.005); NA fat (control 3.2 mg/kg fat)	0.58	1.20	1.15	0.67	1.02 6 wk	0.79 6 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
			1.01 mg/kg	<0.005 mg/kg liver; 105.86 mg/kg fat	0.87	0.92	1.10	0.96	0.94 6 wk	1.24
			1.36 mg/kg	7.25 mg/kg liver; 128.63 mg/kg fat	1.16	0.66	0.75	0.87	0.90 6 wk	1.57
11	Clophen A50 product; TEQ calculated by WHO TEFs	6 month	PCB 0.77 mg/kg (control 0.01 mg/kg) TEQ 22 pg/g		0.96	1.20	1.30	1.24	0.99 birth	
			PCB 2.31 mg/kg TEQ 65 pg/g		0.97	1.04	0.95	0.92	0.82 birth	
		18 month	PCB 0.77 mg/kg TEQ 22 pg/g (NOAEC TEQ 3 pg/g)	11 mg/kg lipid muscle (control <1 mg/kg)	0.95	1.22	1.34	1.27	0.90 birth 0.69 2 wk 0.67 5 wk	0.49 2 wk
			PCB 2.31 mg/kg TEQ 65 pg/g	54 mg/kg	0.42	0.80	0.45	0.20	0.75 birth	0 2 wk

Ref	Exposure				Relative Response Compared to Control					
	Chemical & Source	Exposure Duration	Dietary Conc	Tissue Conc	whelped ♀ / mated ♀	total kits / whelped ♀	live kits / whelped ♀	live kits / mated ♀	kit BW, time	kit survival, time
12	reported as PCB (Aroclor not specified); Baltic herring	5.3 month before mating + exposure during mating; TEQ not specified ("internat-ional" TEFs)	PCB 0.36 mg/kg (control 0.024 mg/kg) TEQ 26 pg/g (control 2 pg/g)		1.00	0.92	0.92	0.92	0.87–0.90 10 d 0.87–0.89 50 d	
	A1242 product added to freshwater smelt	5.3 month before mating, control exposure during mating	PCB 2.88 mg/kg TEQ 157 pg/g		0.80	0.76	0.73	0.58	0.78-0.81 10 d 0.95–1.01 50 d	

Notes for Table 4.

Ref - references [abbreviated reference used in the figures and Table 2 in brackets]:

1) Platonow and Karstad. 1973. [Platonow73]
2) Aulerich and Ringer. 1977. [Aulerich77]
3) Jensen 1977. [Jensen77]
4) Bleavins, et al. 1980 [Bleavins80]
5) Hornshaw, et al. 1983. [Hornshw83]
6) Wren, et al. 1987 [Wren87]
7) Kihiström, et al. 1992. [Kihistrm92]
8) Heaton, et al. 1995a, 1995b, and Tillitt, et al. 1996. [Heaton95]

9) Restum, et al. 1998, Shipp, et al. 1998, and Tillitt, et al. 1996. [Restum98]
10) Halbrook, et al. 1999. [Halbrok99]
11) Brunström, et al. 2001. [Brunstm01]
12) Käkelä, et al. 2002. [Kakela02]

Relative Response Compared to Control = treatment response / control response

Source: product is commercial product mixed with food; field is field-contaminated biota prepared as food

TEQ for Restum, et al. (1998) is based on the following regression of total PCB (mg/kg) and H4IIE-bioassay TEQ (pg/g) (data from Tillitt, et al. 1996):

$$TEQ = (25.735 * PCB) + 0.703 \quad r^2 = 1.0, p = 0.005, \text{ for PCB range } 0.015–1.53 \text{ mg/kg}$$

Table 5. Chicken PCB Toxicity Studies

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
1	A1242 product	chicken (white leghorn)	6 wk	1.34				0.10, 6 wk			
				3.35				0, 6 wk			
		chicken (broiler)		1.34				0.09, 6 wk			
				3.35				0.07, 6 wk			
2	A1242 product	chicken (white leghorn)	6 wk	0.34 (control NA)	0.62 mg/kg 6 wk	0.92, 6 wk		1.03, 6 wk			
				0.67	1.35 mg/kg 6 wk	0.36 6 wk		0.82 6 wk			
				1.34	2.26 mg/kg 6 wk	0.41 6 wk		0.55 6 wk			
				2.68	2.8 mg/kg 6 wk	0.77 6 wk		0 6 wk			
				5.36	10.01 mg/kg 6 wk	0.90 6 wk		0 6 wk			
3	A1254 product	chicken (white leghorn)	14 wk	0.34 (control NA)	5.5 mg/kg (max.) 2-14 wk	0.87 1-14 wk	0.98 1-14 wk	1 1-14 wk			
			39 wk	0.34	7.5 mg/kg (max.) 26-35 wk	0.80 26-39 wk	0.74 34-39 wk	1 1-39 wk			
			14 wk	3.35	50 mg/kg (max.) 2-14 wk	0.75 1-14 wk	1.05 1-14 wk	0 3-6 wk			

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
4	A1254 product	chicken (white leghorn)	6 wk	5.5 (control NA)	10 mg/kg 1 wk; 24 mg/kg 2 wk; 36.4 mg/kg 3 wk; (control NA)	1.02 1-6 wk	1.05 1-6 wk	0.41 2 wk; 0 3-6 wk			
5	A1221 product	chicken (white leghorn)	9 wk	1.30 (control NA)	<1 mg/kg 9 wk	1 0-9 wk		0.99 0-9 wk	0.98 6-9 wk	1	
	A1232 product			1.34	2.5 mg/kg 9 wk	0.91 0-9 wk		0.60 0-9 wk 0.43 8 wk	0.85 6-9 wk	0.93	
	A1242 product			0.12		0.95 0-9 wk		0.98 0-9 wk	0.98 6-9 wk	0.99	
				1.21	14 mg/kg 9 wk	0.85 0-9 wk		0.20 0-9 wk 0.10 8 wk	0.71 6-9 wk	0.93	
	A1248 product			0.12		0.97 0-9 wk		0.99 0-9 wk	0.94 6-9 wk	0.99	
				1.21	10 mg/kg 9 wk	0.85 0-9 wk		0.13 0-9 wk 0.09 8 wk	0.67 6-9 wk	0.44	

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
	A1254 product			0.13		0.97 0-9 wk		0.96 0-9 wk	0.93 6-9 wk	1	
				1.22	12 mg/kg	0.90 0-9 wk		0.86 0-9 wk 0.74 8 wk	0.87 6-9 wk	0.95	
	A1268 product			1.28	23 mg/kg	0.94 0-9 wk		0.98 0-9 wk	0.96 6-9 wk	1	
6	A1232 product	chicken (white leghorn)	8 wk	0.67 (control NA)				0.86 8 wk			
				1.34				0.57, 8 wk			
	A1242 product			0.34				0.84, 0-8 wk			0.94
				0.67				0.74, 0-8 wk 0.51, 8 wk			0.93
				1.34				0.31, 0-8 wk 0.06, 8 wk			0.90
	A1248 product			0.34				0.96, 0-8 wk			1
				0.67				0.75, 0-8 wk 0.42, 8 wk			0.97
				1.34				0.24, 0-8 wk 0.06, 8 wk			0.89

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
7	A1248 product	chicken (white leghorn)	8 wk	0.03 (control NA)	0.16 mg/kg 4 wk; 0.22 mg/kg 8 wk	0.99 8 wk		1.01 4 wk 1.01 8 wk			
				0.07	0.33 mg/kg 4 wk; 0.41 mg/kg 8 wk	1.03 8 wk		0.98 4 wk 1.04 8 wk			
				0.67	2.2 mg/kg 4 wk; 3 mg/kg 8 wk	0.92 8 wk		0.73 4 wk 0.55 8 wk			
				1.34	4.5 mg/kg 4 wk; 7 mg/kg 8 wk	0.87 8 wk		0.03 4 wk 0.03 8 wk			
8	reported as A1242, 1248, 1254 and 1260; H4IIE bioassay TEQ; Saginaw Bay carp	chicken (white leghorn)	8 wk	PCB 0.04 (control 0.016); TEQ 1.4 ng/kg-d (control 0.2)	4 mg/kg 4-8 wk (control 1 mg/kg)	1.37 4-8 wk	0.99 4-8 wk	1.05 4-8 wk	1.0 hatch		0.93 -1 to 8 wk
				PCB 0.36; TEQ 3.2	26 mg/kg 4-8 wk	1.63 4-8 wk	1.28 4-8 wk	0.82 4-8 wk	1.1 hatch		0.72 -1 to 8 wk

Ref	Exposure					Relative Response Compared to Control					
	Chemical, Source	Species	Exposure Duration	Dose to Hen (mg/kg-d)	Egg Conc (whole ww)	Egg Productivity	Egg Fertility	Hatchability	Chick BW	Chick Survival	Chick Normality
9	A1242 product	chicken eggs (white leghorn)	injected in yolk		0.02 mg/kg (control NA)				1.08 embryo		
					0.24 mg/kg				1.07 embryo		
					2.44 mg/kg				0.93 embryo		
	A1254 product				0.02 mg/kg				1.03 embryo		
					0.24 mg/kg				1.02 embryo		
					2.44 mg/kg				0.92 embryo		

Notes for Table 5.

Ref - references [abbreviated reference used in the figures and Table 2 in brackets]:

1) Briggs and Harris. 1972. [Briggs72]
2) Britton and Huston. 1973. [Britton73]
3) Platonow and Reinhart. 1973. [Platonw73]
4) Tumasonis, et al. 1973. [Tumas73]
5) Lillie, et al. 1974 and Cecil, et al. 1974. [Lillie/Cecil74 or Lillie/C74]
6) Lillie, et al. 1975. [Lillie75]
7) Scott 1977. [Scott77]
8) Summer, et al. 1996a., 1996b. [Summer96]
9) Gould, et al. 1997. [Gould97]

Exposures occur through contaminated feed except for Tumasonis, et al. (1973) through contaminated water, and Gould, et al. (1997) through yolk injection.

Relative Response Compared to Control = treatment response / control response

Source: product is commercial product mixed with feed or in water; field is field-contaminated biota prepared as feed

Dose: Calculated from experimental data when available. Generic calculation based on a white leghorn hen food ingestion rate of 0.067 kg feed/kg_{BW}-d (Medway and Kare 1959 cited in USEPA 1995a).

Egg Concentration: Yolk concentration is converted to whole-egg concentration by multiplying by 0.364 (Southerland and Rahn 1987 as cited in Hoffman, et al. 1996).

Chick normality is the proportion of chicks without deformities (= 1 - deformity rate)

Table 6. Summary of Mink PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary PCB conc. mg/kg ww	Treatment name	Chemical source	Dietary TEQ conc. pg/g ww	TEQ source	Exposure duration month	Breeding seasons exposed	Generations exposed	Tissue	Tissue residue PCB conc. mg/kg ww	Tissue residue Lipid cont. % ww	Tissue residue PCB conc. mg/kg lw	Tissue residue TEQ conc. ww	Whelp frequency Control %	Whelp frequency Treatment %	Whelp frequency RR ratio	Whelp freq. source
Platonow73	A1254	0.64		field			5.2	1	1	liver, muscle	1.23, 0.97							
Platonow73	A1254	3.57		field			3.4	1	1	liver, muscle	11.99, 3.31				NA	0	0.00	text p 393
Aulerich77	A1242	2		product			9.7	1	1						100	100	1.00	table 10
Aulerich77	A1254	1		product			4.2	1	1						100	80	0.80	table 9
Aulerich77	A1254	2		product			9.7	1	1						100	29	0.29	table 10
Aulerich77	A1254	5		product			4.2	1	1						100	25	0.25	table 9
Jensen77	NA	3.3	Group B	NA			2.2	1	1	adipose			86		92	73	0.79	table 1
Jensen77	NA	11	Goup C	NA			2.2	1	1	adipose			280		92	0	0.00	table 1
Bleavins80	A1242	5		product			8.1	1	1						76.2	0	0.00	table 2
Bleavins80	A1242	10		product			8.1	1	1						76.2	0	0.00	table 2
Hornshw83	A1254	0.21	alewife	field			7	1	1	adipose			8.1		90	83	0.92	table 3
Hornshw83	A1254	0.48	whitefish	field			7	1	1	adipose			13		90	80	0.89	table 3
Hornshw83	A1254	0.63	sucker	field			7	1	1	adipose			10		90	90	1.00	table 3
Hornshw83	A1254	0.69	perch	field			7	1	1	adipose			13		90	82	0.91	table 3
Hornshw83	A1254	1.5	carp	field			7	1	1	adipose			37		90	27	0.30	table 3
Hornshw83	A1254	0.66	perch/sucker	field			7	1	1						86	50	0.58	table 3
Wren87	A1254	1	PCB	product			6.1	1	1	liver	2.8				93	92	0.99	87b table 2
Kihistrm92	A50	12	Group 2	product			3	1	1	muscle	3.98	2.2	181.00		90	10	0.11	table 2
Kihistrm92	A1254	10	Group 9	product			3	1	1	muscle	1.33	1.8	74.00		89	30	0.34	table 2
Heaton95	PCB	0.72	10 % carp	field	19.4	H4IIE	6	1	1	liver	2.2			495	50	50	1.00	p 335, table 2
Heaton95	PCB	1.53	20 % carp	field	40	H4IIE	6	1	1	liver	3.1			439	50	50	1.00	p 335, table 2
Heaton95	PCB	2.56	30 % carp	field	80.8	H4IIE	6	1	1	liver	6.3			656	50	50	1.00	p 335, table 2
Restum98	PCB	0.25	P1 0.25 to F1-1	field	7.1	H4IIE	6	1	1						69	94	1.36	table 6
Restum98	PCB	0.5	P1 0.5 to F1-1	field	13.6	H4IIE	6	1	1						69	93	1.35	table 6
Restum98	PCB	1	P1 1.0 to F1-1	field	26.4	H4IIE	6	1	1						69	80	1.16	table 6
Restum98	PCB	0.25	P1 0.25-0.25 to F1-2	field	7.1	H4IIE	16	2	1	liver	0.98				86	88	1.02	table 6
Restum98	PCB	0.5	P1 0.5-0.5 to F1-2	field	13.6	H4IIE	16	2	1	liver	0.89				86	67	0.78	table 6
Restum98	PCB	1	P1 1.0-1.0 to F1-2	field	26.4	H4IIE	16	2	1	liver	1.57				86	57	0.66	table 6
Restum98	PCB	0.25	F1-1 0.25-0.25 to F2	field	7.1	H4IIE	12	2	2	liver	0.63				79	67	0.85	table 6
Restum98	PCB	0.5	F1-1 0.5-0.5 to F2	field	13.6	H4IIE	12	2	2	liver	0.96				79	60	0.76	table 6
Restum98	PCB	1	F1-1 1.0-1.0 to F2	field	26.4	H4IIE	12	2	2	liver	1.47				79	50	0.63	table 6
Halbrok99	A1260	0.52	Diet C	field			7	1	1	liver	<0.005				86	50	0.58	text p 652, table 2
Halbrok99	A1260	1.01	Diet D	field			7	1	1	liver, fat	<0.005		105.86		86	75	0.87	text p 652, table 2
Halbrok99	A1260	1.36	Diet E	field			7	1	1	liver, fat	7.25		128.63		86	100	1.16	text p 652, table 2
Brunstm01	A50	0.77	A50 low	product	22	WHO	6	1	1						93	89	0.96	table 3
Brunstm01	A50	2.31	A50 high	product	65	WHO	6	1	1						93	90	0.97	table 3
Brunstm01	A50	0.77	A50 low	product	22	WHO	18	2	1	muscle	0.26	2.4	11		93	88	0.95	table 5
Brunstm01	A50	2.31	A50 high	product	65	WHO	18	2	1	muscle	1.30	2.4	54		93	39	0.42	table 5
Kakela02	PCB	0.36	Baltic herring	field	26	NA	5.3	1	1						100	100	1.00	table 3
Kakela02	A1242	2.88	Smelt PCB	product	157	NA	5.3	1	1						100	80	0.80	table 3

Notes:
Treatment data only, control data excluded (control RR = 1.0 by definition)
TEQ source - H4IIE - rat hepatoma cell bioassay; WHO - Van den Berg, et al. (1998)
Exposure duration - month = days / 30.5 or weeks / 4; PCB - sum of multiple Aroclors; NA - not available
RR - relative response = treatment response / control response
Default Live kits/mated female = Live kits/whelped female * fraction of females whelped
Plantonow73 - Treatment 0.64 Live kits/mated female = 3 kits / 10 females surviving (2 deaths out of 12 during breeding)
Jensen77 - PCB type or source not identified; Live kits/whelped female = No. of whelps born/pregnant female - number of stillbirths/bitch
Hornshaw83 - Tissue residue for February 1980, mean values
Kihlstrm92 - Dietary PCB conc. = 2 mg A50/d or 1.64 mg A1254/d / 0.17 kg food/d (p. 564); Table 2 Stillborn should be 1 (not 100) for Group 2 (fig 4)
Heaton95 - Liver conc. from Tillitt, et al. 96 (Table 4)
Restum98 - Treatment name is parental designation to offspring designation; TEQ interpolated from Tillitt, et al. 96 (Tables 1 and 2)
Restum98 - Live kits/whelped female = Survivability at birth * Litter size
Restum98 - Kit bodyweight in order of male, female kit; -- no survivors; RR is the unweighted mean of male and female RRs, or single sex RR if only one sex survived
Halbrook99 - Diet A is used for control; Kit survival = (Alive at 6 weeks / Born alive) * 100
Brunstm01 - Dietary PCB conc. = 0.1 or 0.3 mg A50/d / 0.13 kg/d food ration (p. 2319)
Kakela02 - Smelt PCB treatment was exposed for 21 wk before breeding, then switched to control diet during breeding
Kakela02 - Dietary PCB conc. = Sum PCB per day / Average food consumption; Kit bodyweight in order of male kit, female kit; RR is unweighted mean
Kakela02 - Live kits/whelped female = ((Kits/mother * surviving females) - Dead kits) / surviving females; TEQ - "International" TEFs but no date is given

Table 6. Summary of Mink PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary PCB conc. mg/kg ww	Treatment name	Total kits / whelped female Control number	Treatment number	RR ratio	Total kits / whelped source	Live kits / whelped female Control number	Treatment number	RR ratio	Live kits / whelped source	Live kits / mated female Control number	Treatment number	RR ratio	Live kits / mated source	Kit bodyweight 0-1 wk Control g	Treatment g	RR ratio
Platonow73	A1254	0.64										1.8	0.3	0.17	text p 393, 398			
Platonow73	A1254	3.57		NA	0	0.00	text p 393	NA	0	0.00	text p 393	1.8	0	0.00	text p 393, 398			
Aulerich77	A1242	2		4.1	5.6	1.37	table 10	3.5	5	1.43	table 10	3.5	5	1.43	table 10	9.9	9.3	0.94
Aulerich77	A1254	1		6	5.4	0.90	table 9	5.1	4.4	0.86	table 9	5.1	3.5	0.69	table 9			
Aulerich77	A1254	2		4.1	1	0.24	table 10	3.5	0.5	0.14	table 10	3.5	0.14	0.04	table 10	9.9	5.4	0.55
Aulerich77	A1254	5		6	3	0.50	table 9	5.1	1	0.20	table 9	5.1	0.25	0.05	table 9			
Jensen77	NA	3.3	Group B	5.1	2.9	0.57	table 1	4.6	0.9	0.20	text, table 1	4.2	0.7	0.17	text, table 1	9.4	6.8	0.72
Jensen77	NA	11	Goup C	5.1	0	0.00	table 1	4.6	0	0.00	text, table 1	4.2	0	0.00	text, table 1			
Bleavins80	A1242	5		5.8	0	0.00	table 2	4.9	0	0.00	table 2	3.8	0	0.00	table 2			
Bleavins80	A1242	10		5.8	0	0.00	table 2	4.9	0	0.00	table 2	3.8	0	0.00	table 2			
Hornshw83	A1254	0.21	alewife	5.4	6.2	1.15	table 3	4.2	5.3	1.26	table 3	3.8	4.2	1.11	table 3	8.3	8.4	1.01
Hornshw83	A1254	0.48	whitefish	5.4	4.9	0.91	table 3	4.2	4	0.95	table 3	3.8	3.2	0.84	table 3	8.3	8.5	1.02
Hornshw83	A1254	0.63	sucker	5.4	4.3	0.80	table 3	4.2	2.8	0.67	table 3	3.8	2.5	0.66	table 3	8.3	8.7	1.05
Hornshw83	A1254	0.69	perch	5.4	5	0.93	table 3	4.2	3.7	0.88	table 3	3.8	3	0.79	table 3	8.3	8.1	0.98
Hornshw83	A1254	1.5	carp	5.4	3	0.56	table 3	4.2	0	0.00	table 3	3.8	0	0.00	table 3			
Hornshw83	A1254	0.66	perch/sucker	5.4	2	0.37	table 3	5.2	1	0.19	table 3	4.4	0.5	0.11	table 3	9	7.7	0.86
Wren87	A1254	1	PCB	6.9	7.5	1.09	87b table 2	5.8	6.7	1.16	87b table 2	5.4	6.2	1.15	87b table 2	28.1	21.6	0.77
Kihistrm92	A50	12	Group 2	8.1	1	0.12	table 2	5.3	0	0.00	table 2	4.8	0	0.00	table 2			
Kihistrm92	A1254	10	Group 9	5	3.3	0.66	table 2	4.3	0	0.00	table 2	3.7	0	0.00	table 2			
Heaton95	PCB	0.72	10 % carp	5.7	5.3	0.93	table 2	5	3.8	0.76	table 2	2.5	1.9	0.76	p 335, table 2	10.5	9.76	0.93
Heaton95	PCB	1.53	20 % carp	5.7	5.8	1.02	table 2	5	4.8	0.96	table 2	2.5	2.4	0.96	p 335, table 2	10.5	8.66	0.82
Heaton95	PCB	2.56	30 % carp	5.7	3.3	0.58	table 2	5	0.7	0.14	table 2	2.5	0.35	0.14	p 335, table 2	10.5	7.49	0.71
Restum98	PCB	0.25	P1 0.25 to F1-1	5	5.8	1.16	table 6	4.7	5.6	1.19	tables 6, 7	3.2	5.3	1.66	table 6	10, 9.2	9.3, 8.7	0.94
Restum98	PCB	0.5	P1 0.5 to F1-1	5	5.1	1.02	table 6	4.7	4.3	0.91	tables 6, 7	3.2	4	1.25	table 6	10, 9.2	8.7, 7.7	0.86
Restum98	PCB	1	P1 1.0 to F1-1	5	5.1	1.02	table 6	4.7	3.6	0.77	tables 6, 7	3.2	2.9	0.91	table 6	10, 9.2	7.5, 7.3	0.77
Restum98	PCB	0.25	P1 0.25-0.25 to F1-2	6.3	6	0.95	table 6	5.6	5.4	0.96	tables 6, 7	4.8	4.7	0.98	table 6	11.1, 9.9	9.8, 10.8	0.99
Restum98	PCB	0.5	P1 0.5-0.5 to F1-2	6.3	5.8	0.92	table 6	5.6	4.5	0.80	tables 6, 7	4.8	3	0.63	table 6	11.1, 9.9	8.6, 8.0	0.79
Restum98	PCB	1	P1 1.0-1.0 to F1-2	6.3	4	0.63	table 6	5.6	3.3	0.59	tables 6, 7	4.8	1.9	0.40	table 6	11.1, 9.9	8.1, 7.3	0.74
Restum98	PCB	0.25	F1-1 0.25-0.25 to F2	5.7	6	1.05	table 6	5.5	5.3	0.96	tables 6, 7	4.3	3.6	0.84	table 6	9.8, 9.2	8.5, 8.0	0.87
Restum98	PCB	0.5	F1-1 0.5-0.5 to F2	5.7	5	0.88	table 6	5.5	1.7	0.31	tables 6, 7	4.3	1	0.23	table 6	9.8, 9.2	7.2, 5.9	0.69
Restum98	PCB	1	F1-1 1.0-1.0 to F2	5.7	3	0.53	table 6	5.5	0.5	0.09	tables 6, 7	4.3	0.3	0.07	table 6	9.8, 9.2	5.0, 5.5	0.56
Halbrok99	A1260	0.52	Diet C	6.5	7.8	1.20	table 2	5.2	6	1.15	table 2	4.5	3	0.67	text p 652, table 2			
Halbrok99	A1260	1.01	Diet D	6.5	6	0.92	table 2	5.2	5.7	1.10	table 2	4.5	4.3	0.96	text p 652, table 2			
Halbrok99	A1260	1.36	Diet E	6.5	4.3	0.66	table 2	5.2	3.9	0.75	table 2	4.5	3.9	0.87	text p 652, table 2			
Brunstm01	A50	0.77	A50 low	4.9	5.9	1.20	table 3	4	5.2	1.30	table 3	3.7	4.6	1.24	table 3	9.6	9.5	0.99
Brunstm01	A50	2.31	A50 high	4.9	5.1	1.04	table 3	4	3.8	0.95	table 3	3.7	3.4	0.92	table 3	9.6	7.9	0.82
Brunstm01	A50	0.77	A50 low	5.1	6.2	1.22	table 5	4.4	5.9	1.34	table 5	4.1	5.2	1.27	table 5	8.9	8	0.90
Brunstm01	A50	2.31	A50 high	5.1	4.1	0.80	table 5	4.4	2	0.45	table 5	4.1	0.8	0.20	table 5	8.9	6.7	0.75
Kakela02	PCB	0.36	Baltic herring	6.6	6.1	0.92	table 3	6.6	6.1	0.92	table 3	6.6	6.1	0.92	table 3			
Kakela02	A1242	2.88	Smelt PCB	6.6	5	0.76	table 3	6.6	4.8	0.73	table 3	6.6	3.8	0.58	table 3			

Table 6. Summary of Mink PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary PCB conc. mg/kg ww	Treatment name	Kit bodyweight 2-3 wk Control g	Kit bodyweight 2-3 wk Treatment g	Kit bodyweight 2-3 wk RR ratio	Kit bodyweight 4-6 wk Control g	Kit bodyweight 4-6 wk Treatment g	Kit bodyweight 4-6 wk RR ratio	Kit bodyweight source	Kit survival Control %	Kit survival Treatment %	Kit survival RR ratio	Kit survival source
Platonow73	A1254	0.64									NA	0	0.00	text p 393
Platonow73	A1254	3.57												
Aulerich77	A1242	2								table 10	64	91	1.42	table 10
Aulerich77	A1254	1												
Aulerich77	A1254	2								table 10	64	0	0.00	table 10
Aulerich77	A1254	5												
Jensen77	NA	3.3	Group B							text	82	17	0.21	text
Jensen77	NA	11	Goup C											
Bleavins80	A1242	5												
Bleavins80	A1242	10												
Hornshw83	A1254	0.21	alewife				122	124	1.02	table 4	55	51	0.93	table 3
Hornshw83	A1254	0.48	whitefish				122	107	0.88	table 4	55	28	0.51	table 3
Hornshw83	A1254	0.63	sucker				122	111	0.91	table 4	55	40	0.73	table 3
Hornshw83	A1254	0.69	perch				122	98	0.80	table 4	55	36	0.65	table 3
Hornshw83	A1254	1.5	carp											
Hornshw83	A1254	0.66	perch/sucker							table 4	65	0	0.00	table 3
Wren87	A1254	1	PCB	107.3	80.2	0.75	227.8	161.2	0.71	87b table 4	72	72.2	1.00	87b table 2
Kihistrm92	A50	12	Group 2											
Kihistrm92	A1254	10	Group 9											
Heaton95	PCB	0.72	10 % carp	98.7	66.1	0.67	248	197	0.79	table 3	85	28	0.33	table3
Heaton95	PCB	1.53	20 % carp	98.7	65.8	0.67	248	101	0.41	table 3	85	11	0.13	table3
Heaton95	PCB	2.56	30 % carp							table 3	85	0	0.00	table3
Restum98	PCB	0.25	P1 0.25 to F1-1	113, 99	89, 88	0.84	293, 253	220, 214	0.80	table 8	72.7	67.8	0.93	table 7 wk 6
Restum98	PCB	0.5	P1 0.5 to F1-1	113, 99	76, 74	0.71	293, 253	200, 165	0.67	table 8	72.7	52.5	0.72	table 7 wk 6
Restum98	PCB	1	P1 1.0 to F1-1	113, 99	58, 58	0.55	293, 253	102, 125	0.42	table 8	72.7	23	0.32	table 7 wk 6
Restum98	PCB	0.25	P1 0.25-0.25 to F1-2	116, 110	106, 96	0.89	340, 304	312, 280	0.92	table 9	80.3	76.2	0.95	table 7 wk 6
Restum98	PCB	0.5	P1 0.5-0.5 to F1-2	116, 110	78, 72	0.66	340, 304	317, --	0.93	table 9	80.3	4.4	0.05	table 7 wk 6
Restum98	PCB	1	P1 1.0-1.0 to F1-2	116, 110	69, 55	0.55	340, 304	223, 182	0.63	table 9	80.3	12.5	0.16	table 7 wk 6
Restum98	PCB	0.25	F1-1 0.25-0.25 to F2	116, 106	128, 109	1.07	380, 326	361, 291	0.92	table 10	73	58.3	0.80	table 7 wk 6
Restum98	PCB	0.5	F1-1 0.5-0.5 to F2	116, 106	--, 45	0.42	380, 326	--, 177	0.54	table 10	73	13.3	0.18	table 7 wk 6
Restum98	PCB	1	F1-1 1.0-1.0 to F2							table 10	73	0	0.00	table 7 wk 6
Halbrok99	A1260	0.52	Diet C				328	333	1.02	table 2	63.5	50	0.79	table 2
Halbrok99	A1260	1.01	Diet D				328	307	0.94	table 2	63.5	78.9	1.24	table 2
Halbrok99	A1260	1.36	Diet E				328	295	0.90	table 2	63.5	100	1.57	table 2
Brunstm01	A50	0.77	A50 low							table 3				
Brunstm01	A50	2.31	A50 high							table 3				
Brunstm01	A50	0.77	A50 low	70	48	0.69	258	173	0.67	table 5, fig 2	73	36	0.49	text p 2322
Brunstm01	A50	2.31	A50 high							table 5	73	0	0.00	text p 2322
Kakela02	PCB	0.36	Baltic herring	63, 58	55, 52	0.89	566, 505	501, 439	0.88	table 3				
Kakela02	A1242	2.88	Smelt PCB	63, 58	49, 47	0.80	566, 505	573, 481	0.96	table 3				

Table 7. Summary of Chicken PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary conc. mg/kg fw	Food ingestion kg/kgbw fw	Dose mg/kg-d	Exposure duration wk	Yolk conc. mg/kg fw	Whole egg conc. mg/kg fw	Egg conc. source	Control # or %	Productivity Treatment # or %	RR ratio	Productivity source	Control %	Fertility Treatment %	RR ratio	Fertility source
Briggs72	A1242	20	0.067	1.34	6											
Briggs72	A1242	50	0.067	3.35	6											
Briggs72	A1242	20	0.067	1.34	6											
Briggs72	A1242	50	0.067	3.35	6											
Britton73	A1242	5	0.067	0.34	6	1.7	0.62	table 3 wk 6	61	56	0.92	table 1 wk 6				
Britton73	A1242	10	0.067	0.67	6	3.7	1.35	table 3 wk 6	61	22	0.36	table 1 wk 6				
Britton73	A1242	20	0.067	1.34	6	6.2	2.26	table 3 wk 6	61	25	0.41	table 1 wk 6				
Britton73	A1242	40	0.067	2.68	6	7.7	2.80	table 3 wk 6	61	47	0.77	table 1 wk 6				
Britton73	A1242	80	0.067	5.36	6	27.5	10.01	table 3 wk 6	61	55	0.90	table 1 wk 6				
Platonw73	A1254	5	0.067	0.34	14		5.5	fig 4 max. wk 12	82.7	72	0.87	text p 343 wk 1-14	85.5	83.6	0.98	text p 344 wk 1-14
Platonw73	A1254	5	0.067	0.34	39		7.5	fig 4 max. wk 26	72	57.5	0.80	text p 343 wk 26-39	85	63.3	0.74	fig 2 wk 34-39
Platonw73	A1254	50	0.067	3.35	14		50	fig 4 max. wk 12	82.7	62.2	0.75	text p 343 wk 1-14	85.5	89.9	1.05	text p 344 wk 1-14
Tumas73	A1254	50	0.11	5.50	6	100	36.40	fig 2 wk 3	8.6	8.77	1.02	table 1 wk 1-6	92.3	97.2	1.05	table 1 wk 1-6
Lillie/Cecil74	A1221	20	0.0649	1.30	9		<1	Cecil fig 4 wk 9	79.4	79.3	1.00	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1232	20	0.067	1.34	9		2.5	Cecil fig 4 wk 9	79.4	71.9	0.91	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1242	2	0.0615	0.12	9				79.4	75.5	0.95	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1242	20	0.0605	1.21	9		14	Cecil fig 4 wk 9	79.4	67.5	0.85	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1248	2	0.0623	0.12	9				79.4	76.9	0.97	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1248	20	0.0607	1.21	9		10	Cecil fig 4 wk 9	79.4	67.5	0.85	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1254	2	0.0636	0.13	9				79.4	77.1	0.97	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1254	20	0.061	1.22	9		12	Cecil fig 4 wk 9	79.4	71.3	0.90	Lillie table 1 wk 0-9				
Lillie/Cecil74	A1268	20	0.0641	1.28	9		23	Cecil fig 4 wk 9	79.4	74.4	0.94	Lillie table 1 wk 0-9				
Lillie75	A1232	10	0.067	0.67	8											
Lillie75	A1232	20	0.067	1.34	8											
Lillie75	A1242	5	0.067	0.34	8											
Lillie75	A1242	10	0.067	0.67	8											
Lillie75	A1242	20	0.067	1.34	8											
Lillie75	A1248	5	0.067	0.34	8											
Lillie75	A1248	10	0.067	0.67	8											
Lillie75	A1248	20	0.067	1.34	8											
Scott77	A1248	0.5	0.067	0.03	8		0.22	table 1 wk 8	74.5	74	0.99	table 3 wk 8				
Scott77	A1248	1	0.067	0.07	8		0.41	table 1 wk 8	74.5	76.6	1.03	table 3 wk 8				
Scott77	A1248	10	0.067	0.67	8		3	table 1 wk 8	74.5	68.7	0.92	table 3 wk 8				
Scott77	A1248	20	0.067	1.34	8		7	table 1 wk 8	74.5	64.8	0.87	table 3 wk 8				
Summer96	PCB	0.8	0.0553	0.04	8		4	96b table 1 wk 6-10	54	74	1.37	96a table 5 wk 6-10	67	66.6	0.99	96a table 6 wk 6-10
Summer96	PCB	6.6	0.0548	0.36	8		26	96b table 1 wk 6-10	54	88	1.63	96a table 5 wk 6-10	67	85.7	1.28	96a table 6 wk 6-10
Gould97	A1242	yolk inject				0.067	0.02	table 1								
Gould97	A1242	yolk inject				0.67	0.24	table 1								
Gould97	A1242	yolk inject				6.7	2.44	table 1								
Gould97	A1254	yolk inject				0.067	0.02	table 1								
Gould97	A1254	yolk inject				0.67	0.24	table 1								
Gould97	A1254	yolk inject				6.7	2.44	table 1								

Notes:
Default Food ingestion rate - 0.067 kg feed/kgbw-d white leghorn hen (Medway and Kare 1959)
Whole egg conc. = 0.364 yolk conc. (Sotherland and Rahn 1987)
RR - relative response = treatment response / control response; Normality = 1 - deformity
Tumas73 - Dietary conc. is mg/l water conc; Food ingestion rate is l/kgbw-d water ingestion = 0.177 l/hen/d / 1.61 kgbw/hen (p. 314, 315)
Lillie/Cecil74 - Food consumption = treatment food/hen-d (Lillie table 2 wk 0-9) / 1.953 kg mean initial hen bodyweight (Lillie p 727)
Lillie75 - Normality = 100 - % abnormal embryos of fertile eggs
Summer96 - Food ingestion rate - mean for wk 3-10 (96a table 4); Chick deformity recalculated from 96b table 5 (replace rounded percentages)
Gould97 - Yolk injection on day 0 of incubation. Treatment "chick" bodyweight is % difference in 17-d embryo bodyweight compared to control

Table 7. Summary of Chicken PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary conc. mg/kg fw	Control %	Hatchability Treatment %	RR ratio	Hatchability source	Chick Bodyweight Control g	Chick Bodyweight Treatment g	RR ratio	Bodyweight source	Chick Survival Control %	Chick Survival Treatment %	RR ratio	Survival source	Chick Normality (1 - defomity) Control %	Chick Normality (1 - defomity) Treatment %	RR ratio
Briggs72	A1242	20	68.9	7.2	0.10	table 1 wk 6 leghorn											
Briggs72	A1242	50	68.9	0	0.00	table 1 wk 6 leghorn											
Briggs72	A1242	20	65.5	6.2	0.09	table 1 wk 6 broiler											
Briggs72	A1242	50	65.5	4.5	0.07	table 1 wk 6 broiler											
Britton73	A1242	5	91	94	1.03	table 3 wk 6											
Britton73	A1242	10	91	75	0.82	table 3 wk 6											
Britton73	A1242	20	91	50	0.55	table 3 wk 6											
Britton73	A1242	40	91	0	0.00	table 3 wk 6											
Britton73	A1242	80	91	0	0.00	table 3 wk 6											
Platonw73	A1254	5	90	90	1.00	text p 344 wk 1-14											
Platonw73	A1254	5	90	90	1.00	text p 344, wk 1-39											
Platonw73	A1254	50	90	0	0.00	text p 344 wk 2-14											
Tumas73	A1254	50	84.7	0	0.00	table 1 wk 3-6											
Lillie/Cecil74	A1221	20	93.7	93.2	0.99	Lillie table 3 wk 0-9	163	159	0.98	Lillie table 4 wk 6-9	98.4	98.3	1.00	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1232	20	92.4	40	0.43	Cecil fig 1 wk 8	163	139	0.85	Lillie table 4 wk 6-9	98.4	91.9	0.93	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1242	2	93.7	92.2	0.98	Lillie table 3 wk 0-9	163	160	0.98	Lillie table 4 wk 6-9	98.4	97.1	0.99	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1242	20	92.4	9	0.10	Cecil fig 1 wk 8	163	115	0.71	Lillie table 4 wk 6-9	98.4	91.7	0.93	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1248	2	93.7	92.3	0.99	Lillie table 3 wk 0-9	163	153	0.94	Lillie table 4 wk 6-9	98.4	97.5	0.99	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1248	20	92.4	8	0.09	Cecil fig 1 wk 8	163	109	0.67	Lillie table 4 wk 6-9	98.4	43.7	0.44	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1254	2	93.7	89.7	0.96	Lillie table 3 wk 0-9	163	151	0.93	Lillie table 4 wk 6-9	98.4	98.7	1.00	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1254	20	92.4	68	0.74	Cecil fig 1 wk 8	163	141	0.87	Lillie table 4 wk 6-9	98.4	93.7	0.95	Lillie table 4 wk 6-9			
Lillie/Cecil74	A1268	20	93.7	92.2	0.98	Lillie table 3 wk 0-9	163	156	0.96	Lillie table 4 wk 6-9	98.4	98.7	1.00	Lillie table 4 wk 6-9			
Lillie75	A1232	10	90	77	0.86	text p 1554 wk 8											
Lillie75	A1232	20	90	51	0.57	text p 1554 wk 8											
Lillie75	A1242	5	91	76	0.84	table 3 wk 4-8									98	92	0.94
Lillie75	A1242	10	90	46	0.51	text p 1554 wk 8									98	91	0.93
Lillie75	A1242	20	90	5	0.06	text p 1554 wk 8									98	88	0.90
Lillie75	A1248	5	91	87	0.96	table 3 wk 4-8									98	98	1.00
Lillie75	A1248	10	90	38	0.42	text p 1554 wk 8									98	95	0.97
Lillie75	A1248	20	90	5	0.06	text p 1554 wk 8									98	87	0.89
Scott77	A1248	0.5	90.5	91.6	1.01	table 4 wk 8											
Scott77	A1248	1	90.5	93.7	1.04	table 4 wk 8											
Scott77	A1248	10	90.5	50	0.55	table 4 wk 8											
Scott77	A1248	20	90.5	2.4	0.03	table 4 wk 8											
Summer96	PCB	0.8	85.8	90	1.05	96b table 2 wk 6-10	34.49	34.49	1.00	96b table 4 wk 6-10					82.7	76.5	0.93
Summer96	PCB	6.6	85.8	70.2	0.82	96b table 2 wk 6-10	34.49	37.81	1.10	96b table 4 wk 6-10					82.7	59.9	0.72
Gould97	A1242	yolk inject						+8.4 %	1.08	fig 2 (17-d embryo)							
Gould97	A1242	yolk inject						+6.7 %	1.07	fig 2 (17-d embryo)							
Gould97	A1242	yolk inject						-7.0 %	0.93	fig 2 (17-d embryo)							
Gould97	A1254	yolk inject						+2.8 %	1.03	fig 2 (17-d embryo)							
Gould97	A1254	yolk inject						+2.1 %	1.02	fig 2 (17-d embryo)							
Gould97	A1254	yolk inject						-7.7 %	0.92	fig 2 (17-d embryo)							

Table 7. Summary of Chicken PCB Studies and Relative Responses

Lead author Date	Chemical	Dietary conc. mg/kg fw	Normality source
Briggs72	A1242	20	
Briggs72	A1242	50	
Briggs72	A1242	20	
Briggs72	A1242	50	
Britton73	A1242	5	
Britton73	A1242	10	
Britton73	A1242	20	
Britton73	A1242	40	
Britton73	A1242	80	
Platonw73	A1254	5	
Platonw73	A1254	5	
Platonw73	A1254	50	
Tumas73	A1254	50	
Lillie/Cecil74	A1221	20	
Lillie/Cecil74	A1232	20	
Lillie/Cecil74	A1242	2	
Lillie/Cecil74	A1242	20	
Lillie/Cecil74	A1248	2	
Lillie/Cecil74	A1248	20	
Lillie/Cecil74	A1254	2	
Lillie/Cecil74	A1254	20	
Lillie/Cecil74	A1268	20	
Lillie75	A1232	10	
Lillie75	A1232	20	
Lillie75	A1242	5	Table 3
Lillie75	A1242	10	Table 3
Lillie75	A1242	20	Table 3
Lillie75	A1248	5	Table 3
Lillie75	A1248	10	Table 3
Lillie75	A1248	20	Table 3
Scott77	A1248	0.5	
Scott77	A1248	1	
Scott77	A1248	10	
Scott77	A1248	20	
Summer96	PCB	0.8	96b table 5 wk 1-10
Summer96	PCB	6.6	96b table 5 wk 1-10
Gould97	A1242	yolk inject	
Gould97	A1242	yolk inject	
Gould97	A1242	yolk inject	
Gould97	A1254	yolk inject	
Gould97	A1254	yolk inject	
Gould97	A1254	yolk inject	